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A.M.A. JOURNAL OF DISEASES OF CHILDREN

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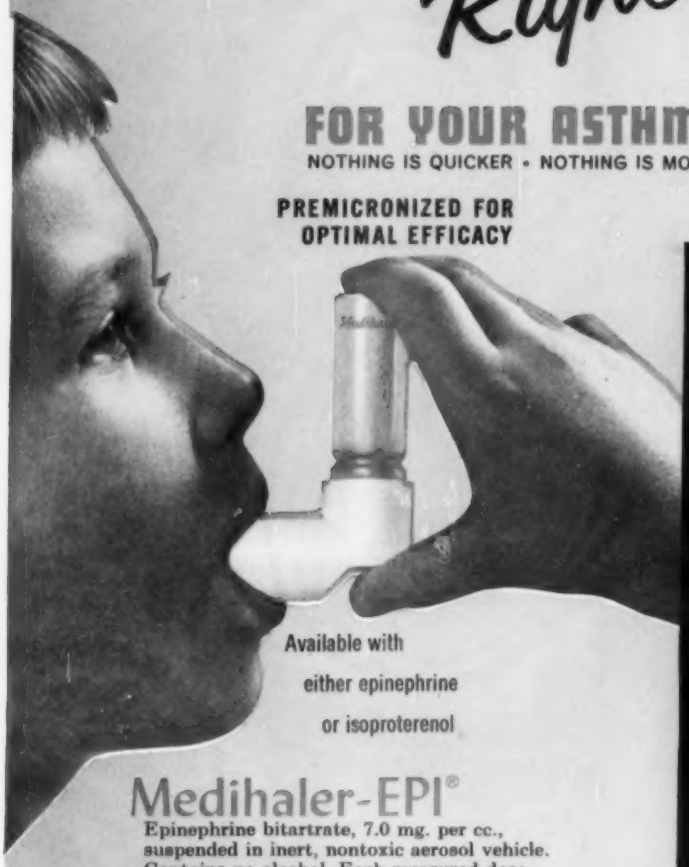

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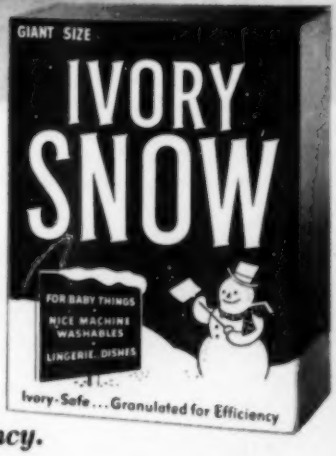

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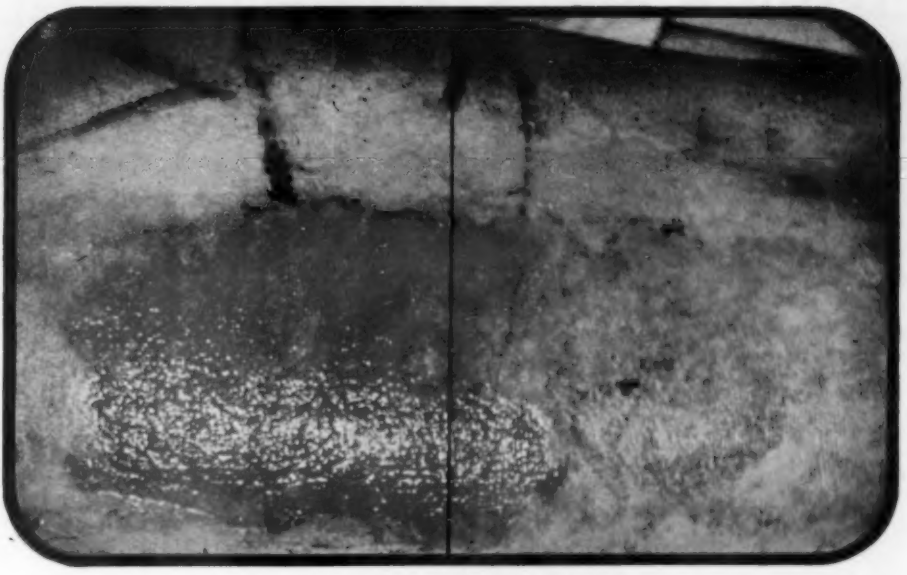

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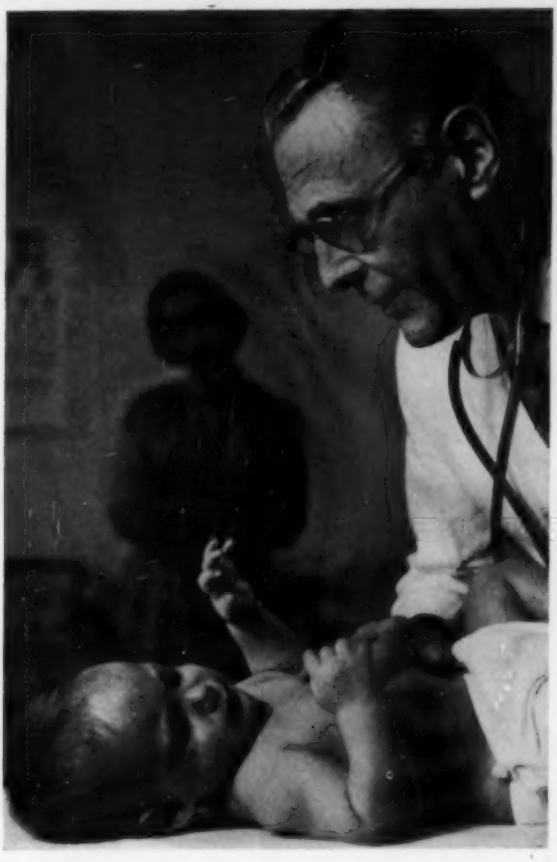

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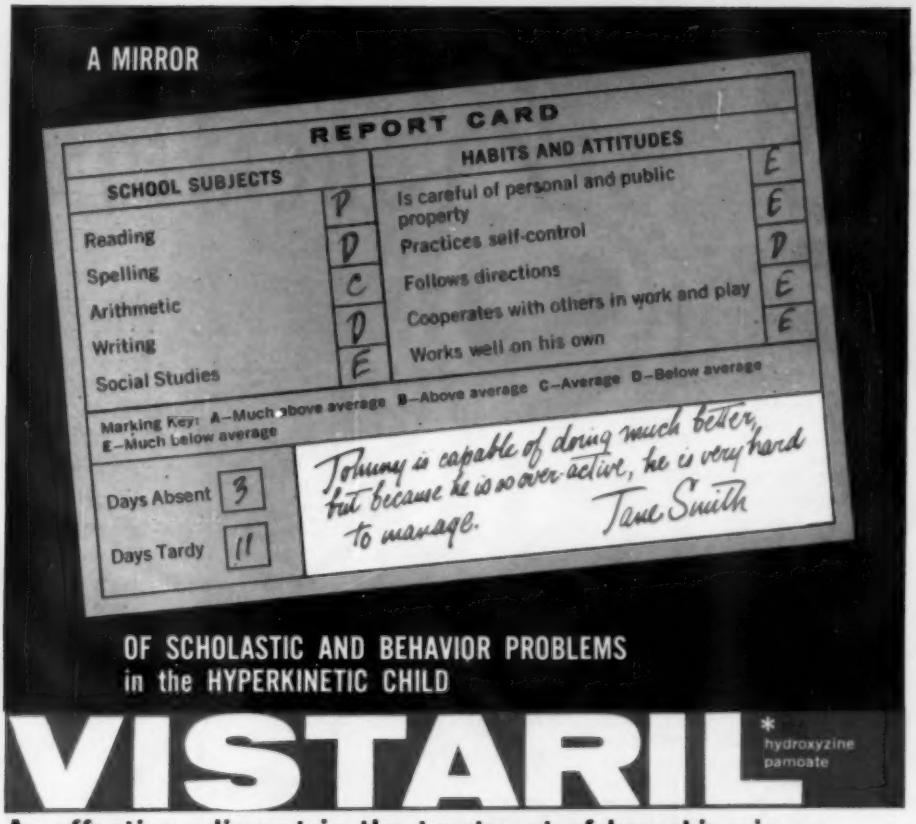

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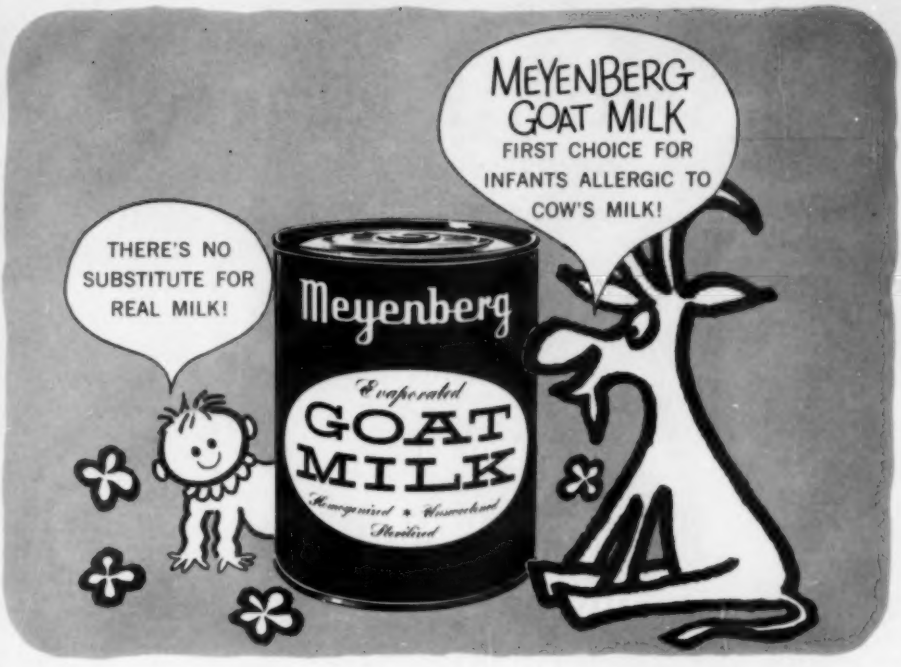

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The Infant of the Diabetic Mother

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I. Introduction

The newborn infant of a diabetic mother presents physiological problems which are unique in clinical medicine. He is considerably larger than would be expected from the duration of the pregnancy. This is usually accompanied by a corresponding increase in the size of the organs within the body. Even if delivered several weeks

before term, he appears to be mature or even postmature. Almost invariably, he exhibits generalized edema, which is marked at birth and disappears after the first few days of life. Despite his large body size and apparent maturity, he behaves much like a premature infant and is very fragile. About a third of such infants die either while in utero during the latter half of pregnancy or in association with respiratory distress during the early neonatal period. After birth, he frequently exhibits unusual anatomical, biochemical, or physiological changes, many of which remain unexplained.

In the three decades since the discovery of insulin, these problems have occupied the attention first of obstetricians, internists, pediatricians, and pathologists and more recently that of endocrinologists, physiologists, and biochemists.[10,62,141,196] Despite a great deal of concerted effort, there has been no clear-cut explanation for these disturbances. It is apparent that we are dealing with a complex problem in which new approaches are needed.

The purpose of the present paper is to evaluate critically from the pediatric viewpoint the previous work which has been done in this field and to add our personal experience with over 900 diabetic pregnancies. It is hoped that such a review will help to separate fact from fiction and to point out directions in which future work might be fruitfully pursued.

II. Case Material

The present series includes a total of 934 pregnancies from the case load of the Joslin Clinic, Boston, between Jan. 1, 1940, and June 30, 1956. The series includes all cases seen in the Clinic during pregnancy and subsequently delivered at the Faulkner Hospital (1940-1950) and the Boston

TABLE 1.—*Total Fetal Wastage in Present Series*

		Abortions (1-18 Wk.)		Previable Deaths (19-28 Wk.)			Viable Deaths (29 Wk. +)		Total Fetal Wastage	
Year	Preg., No.	Therapeutic	Spontaneous	Therapeutic	Intrauterine	Neonatal	Intrauterine	Neonatal	No.	%
1940	23	1	1	0	0	0	1	4	7	30.5
1941	23	0	6	0	0	0	0	2	8	35.0
1942	32	1	5	0	3	0	2	1	12	37.5
1943	40	0	7	0	0	1	7	3	18	45.0
1944	32	1	2	1	1	0	2	5	12	37.5
1945	45	2	4	0	3	0	2	7	18	40.0
1946	63	2	6	0	0	0	7	2	17	27.0
1947	58	2	8	0	2	3	5	4	24	41.0
1948	60	3	9	1	1	0	5	6	25	41.5
1949	65	2	9	3	1	0	5	9	29	44.5
1950(a)	30	3	1	1	3	0	3	3	14	46.5
Total, Faulkner	471	17	58	6	14	4	39	46	184	39
1950(b)	26	1	4	0	0	0	0	1	6	23.0
1951	82	5	5	1	2	2	4	6	25	30.5
1952	58	5	8	0	2	1	1	7	24	41.5
1953	95	3	11	0	0	2	5	10	31	32.5
1954	91	0	10	0	4	2	2	8	26	28.5
1955	73	0	2	0	3	0	3	9	17	23.5
1956(a)	38	2	1	1	3	0	2	6	15	39.5
Total, Boston Lying-in	463	16	41	2	14	7	17	47	144	31
Grand total	934	33	99	8	28	11	56	93	328	35
		132		47			149			

Lying-in Hospital (1950-1956). All of the patients were under the care of a team consisting of an internist, two obstetricians, an anesthetist, and a pediatrician. In order to maintain uniformity of data we have excluded from the series all cases in the two hospitals which were not supervised by the Joslin Clinic team and a few Joslin Clinic patients who were delivered by outside obstetricians in other hospitals.

All of the data to be presented were obtained and independently analyzed by us from hospital records, clinic records, and our own pediatric notes.

Since 1946, one or the other of us has personally attended all deliveries and supervised the pediatric care of the infants during the neonatal period. This represents a combined experience with over 600 infants born of mothers with diabetes mellitus.

The data for the whole series are tabulated by years, as shown in Table 1.

III. General Considerations on Fetal Mortality

A. Historical Background.—Bennewitz,[22] in 1826, was apparently the first to record pregnancy in a diabetic. The patient had suffered from intense thirst and polyuria during three successive pregnancies. Bennewitz states, "the taste of urine resembled beer but was much sweeter" and "the urine contained two ounces of saccharine matter per pound." A second case was published by Lever,[121] in 1847, but it was not until the early part of the present century that Offergeld [162] and Williams [256] were able to present comparatively large series of cases.

Prior to the discovery of insulin, pregnancy in the diabetic was a grave undertaking for both the mother and the child. As a result, such women rarely became pregnant and when pregnancy did occur therapeutic abortion was performed. Very few figures are available on the total fetal wastage during that era. Those reported by Williams [256] and the Joslin Clinic [248] are tabulated in Table 2. They not only are of interest from the historical point of view but also are useful for comparison with present day figures. They show very clearly that the maternal mortality during pregnancy alone accounts for about one-sixth of all fetal wastage and that there is a high incidence of fetal wastage throughout the whole pregnancy. If the infant should perchance be born alive, the clinicians of that era showed little further interest as to whether or not he survived.

B. Fertility.—Prior to the discovery of insulin, women with diabetes mellitus rarely became pregnant. Skipper [210] reported a figure of 2%; Lecorché,[119] 6%, and Parsons, Randall, and Wilder,[188] from the Mayo Clinic, 4%. In 1882, von Noorden [158] undertook a survey of 427 diabetic women and found that pregnancy had occurred in only 5%.

Since the advent of insulin fertility no longer seems to be a problem. Moss and Mulholland [154] reported that 11.6% of diabetic women of childbearing age were or had been pregnant. Paton [169] reported an incidence of 7.3%. This incidence does not differ from that for normal women reported by Hamblen.[89] At the present time, the frequency with which diabetes is encountered among women is variously estimated at from 1 in 50 to 1 in 900, averaging about 1 in 500.[13,62,79,88,182,198] The latter

TABLE 2.—*Fetal Wastage Prior to Insulin Era*

	Total Preg.	Maternal Deaths	Abortions	Stillbirths	Neonatal Deaths *	Live Births	Total Fetal Wastage, %
Williams (to 1909) [256]	82	25	7	20	1	29	65
Joslin (1898–1922) [248]	115	7	28	23	0	57	49
Total	197	32	35	43	1	86	56

* Figures are incomplete because of poor records.

TABLE 3.—*Incidence of Spontaneous Abortions Among Diabetic Mothers*

	Total Preg. *	Spontaneous Abortions	%
Gellis & Hsia	803	127	14.2
Clayton [40]	190	7	3.8
Jones [108]	184	8	4.4
Adams [3]	127	11	8.6
Moss & Mulholland [104]	42	9	21.0
Mengert & Laughlin [101]	39	11	28.0
Patterson & Burnstein [119]	113	24	21.0
Hall & Tillman [63]	119	12	10.0
Total	1,707	209	12.3

* Excluding therapeutic abortions.

figure represents the estimated incidence of diabetes among all women of childbearing age.[132] Certainly, the 934 pregnancies reported in the present series together with nearly 3,000 cases recorded in the literature provide proof that infertility is not a significant problem among women with diabetes.

C. Fetal Mortality During Early Pregnancy.—In reviewing the literature, it is difficult to obtain an accurate estimate of fetal mortality prior to the period of viability. Collection of such information is handicapped by the fact that many of the women do not report early miscarriages or are not followed by the same group throughout the entire pregnancy period. Furthermore, a number of diabetic pregnancies are interrupted because of medical indications.

The information on the spontaneous abortion rate of several of the larger series is tabulated in Table 3. Although the rates are highly variable, the average for the whole group does not significantly differ from the 10% loss among normal women reported by Eastman.[61] Similarly, the proportion of miscarriages (0-18 weeks) and previable deaths (19-28 weeks) in the present series is similar to that estimated by Simons [208] for normal women (χ^2 [1 *d. f.*] = 2.49, P between 0.10 and 0.20). This would suggest that the fetal loss prior to viability is a relatively unimportant cause for the high incidence of fetal mortality.

D. Fetal Mortality During Late Pregnancy.—We next turn to the crucial problem of fetal mortality during the period of viability. Unfortunately, the published literature suffers from a number of defects in the tabulation and interpretation of fetal mortality figures. These include (1) a lack of uniformity in classifying abortions, premature births, and "viable births" (What is listed as an abortion by one group of investigators may be classified as a "viable pregnancy" by another; a small shift between these three categories might produce considerable change in mortality rates); (2) a tendency to exclude certain cases for a variety of reasons; authors frequently will exclude deaths due to "obstetrical cause," congenital anomalies, toxemia, and poor control of diabetes, which might materially reduce the mortality rate in a particular series; (3) a common practice of publishing investigations based on less than 100 cases, with an attempt to appraise various therapeutic effects from such limited data (It is well known that in a series of patients such as this, there are periods when the mortality rate will be unusually high and other periods when it is unusually low. However, over a length of time and with a larger series, these differences tend to balance out. In our own experience, we have on one occasion had 67 consecutive deliveries over an eight-month period without a single death, followed by a half-dozen deaths within the following two weeks.), and (4) a desire to compare differences in mortality between groups of cases without adequate statistical safeguards.

In order to overcome some of these objections, we shall limit the discussion only to women with viable pregnancies, i. e., those with pregnancies of 28 weeks or longer. We have chosen length of gestation rather than weight at birth because it has recently been shown that infants of diabetic mothers with nephritis tend to weigh less than infants of like gestational age born of diabetic mothers without that complication.[164] With use of this criterion, all of the available information on infants of diabetic mothers has been recalculated and divided into the following groups of cases

TABLE 4.—*Fetal Mortality Among Viable Infants (More than Twenty-Eight Weeks) of Diabetic Mothers*

Authors	References	Viable Preg., No.	Deaths			
			Intra-uterine	Neo-natal	Total	%
Group 1(a). Series of more than 50 cases (managed by 1 team)						
Gellis & Hsia (1956)	156, 209, 216, 223, 234, 243-251	768	56	93	149	19
Clayton (1956); Peel & Oakley (1949)	43, 118, 161, 181, 182	325	37	50	87	27
Pedersen (1956)	175-177	265	--	--	58	22
Tolstoi, Given, & Douglas (1953)	83, 235	182	23	25	48	26
Adams (1955)	3, 252, 253	101	8	8	16	16
Pedowitz & Shlevin (1955)	179, 180	73	4	2	6	8
Reis, DeCosta, & Allweiss (1950)	195, 196	59	6	2	8	13
Total		1,773	134	180	372	21
Group 1(b). Series of more than 50 cases (managed by different physicians)						
Jones (1955)	103-105	162	33	16	49	30
Hurwitz & Higano (1952)	98, 99	140	22	10	32	23
Long et al. (1954)	123	118	20	12	32	27
Hall & Tillman (1951)	88, 94	104	17	2	19	18
van Bouwdijk (1951)	238	95	--	--	20	21
Patterson & Burnstein (1949)	64, 170	88	--	--	31	35
Weinstein (1953)	242	73	10	7	17	22
Thosteson (1953)	233	72	8	6	14	19
Flowers & Levit (1954)	73	62	13	6	19	31
Gilbert & Dunlop (1949)	79	59	--	--	24	41
Pease, Smallpiece, & Lennon (1951)	172	58	--	--	20	35
Henley (1947)	93	53	--	--	29	55
Randall (1947)	190, 191	50	6	4	10	20
Total		1,134	129	63	316	28
Group 2. Series of fewer than 50 cases						
Andersson (1950)	7	47	--	--	19	41
Barns & Morgans (1949)	11, 13	40	13	9	22	55
Barns & Morgans (1952)	14	24	3	1	4	17
Basil-Jones (1949)	16	9	2	1	3	33
Bill & Posey (1944)	25	45	7	2	9	20
Brandstrup & Okkels (1938)	32	23	8	5	13	57
Bromberg & Toaff (1950)	34	5	5	0	5	100
Brosset (1945)	35	36	--	--	19	53
Ewald (1945)	65	2	--	--	2	100
Gaspar (1945)	75	49	19	6	25	51
Keitz, Keaty & Hellbaum (1952)	108	30	8	2	10	33
Lavieties et al. (1943)	117	31	8	4	12	39
Mengert & Laughlin (1939)	134	33	4	2	6	18
Moss & Mulholland (1951)	154	33	11	3	14	43
Northmann (1941)	159	5	0	0	0	0
Paalman (1954)	165	12	0	0	0	0
Palmer, Crampton & Barnes (1948)	166, 167	36	2	4	6	17
Paton (1948)	169	38	8	2	10	21
Peckham (1931)	173, 228	17	5	1	6	35
Peterson (1947)	185	46	14	5	19	41
Potter & Adair (1938)	188	15	2	2	4	27
Rike & Fawsett (1948)	198	46	7	2	9	19
Ronsheim (1933)	200	26	13	0	13	50
Sheumack (1949)	203	45	11	5	16	35
Shir (1939)	205	28	4	0	4	14
Skipper (1933)	210	37	--	--	15	41
Wynne-Jones (1949)	260	21	8	2	10	48
Total		779	163	58	275	35
Group 3. Collected series of more than 100 cases						
Kramer (1936)	111, 112	480	164	39	203	42
Peel & Oakley (1951)	182	455	134	49	183	41
Miller, Hurwitz & Kuder (1944)	147	146	30	13	43	29
Medical Research Council (1955)	133	136	16	18	34	25
Skipper (1933)	210	125	--	--	31	44
Total		1,354	344	119	520	38

TABLE 5.—*Summary of Fetal Mortality Statistics in Viable Infants (More than Twenty-Eight Weeks) of Diabetic Mothers* *

	Viable Preg., No.	Deaths				
		Intra-uterine	Neonatal	Unknown	Total	%
A. Nondiabetic infants (48)						
1. All infants	83,764	1,942	1,572	0	3,514	4.2
2. Premature, 5½ lb.	6,883	926	928	0	1,854	26.9
B. Diabetic infants (individual series)						
Group 1(*a*). Series > 50 cases (managed by 1 team)	1,773	134	180	58	372	21
Group 1(*b*). Series >50 cases (managed by different physicians)	1,134	129	63	124	316	27
Group 2. Series<50 cases	779	162	58	55	275	35
Total	3,686	425	301	237	963	26
C. Diabetic infants (collected series)						
Group 3. Series >100 cases	1,354	344	119	57	520	38

* Comparison of A-1 and B totals gives rise to χ^2 of 6,820 and comparison of A-2 and B totals, to χ^2 of 0.61, in each case for 1 *d. f.* Comparison of B-1(*a*) and B-1(*b*) gives rise to χ^2 of 9.65; of B-1(*b*) and B-2, to χ^2 of 8.05, and of B-1+2 and C-3, to χ^2 of 40.21, in each case for 1 *d. f.*

(Table 4): 1. Individual series with more than 50 cases.* These have in turn been subdivided into (*a*) those managed by one team of internists, obstetricians, and pediatricians, and (*b*) those managed by different physicians in the same hospital. 2. Individual series with fewer than 50 cases.† 3. Collected series of more than 100 cases. (Some of these have been reported as part of individual series in Groups 1 and 2 and therefore cannot be regarded as additional new cases.)

These data are summarized and compared with mortality statistics in normal and premature infants born of mothers without diabetes in Table 5. The latter figures are from the city of Birmingham for the years 1947 to 1950, calculated by Crosse,[48] which are reasonably representative.

Using these data, we must first establish that women with diabetes mellitus do, in fact, suffer from greater fetal loss during late pregnancy than does the population as a whole. This can be done by comparing the fetal mortality of the total diabetic experience in Section B with the total Birmingham experience in Section B, Line 1, in Table 5. It can be seen that the fetal mortality is about sixfold greater, and this difference is highly significant (χ^2 [1 *d. f.*] = 6820, *P* less than 0.001). However, if one compares the same total diabetic experience with the premature infants weighing 5½ lb. or less in Section A, Line 2, the difference is not significant (χ^2 [1 *d. f.*] = 0.61, *P* between 0.30-0.50).

We turn next to a comparison of the various series of cases. Despite many claims to the contrary, no one group has been able to achieve better results than another. However, if one compares over-all mortality rate of those managed by a single team (Table 4, Group 1[*a*]) with those managed by several physicians, no one of whom has been responsible for the entire group, (Table 4, Group 1[*b*]) the differences are statistically significant (χ^2 [1 *d. f.*] = 9.65, *P*, 0.005). The fetal mortality of individual series managed by different physicians (Group 1[*b*]) is still significantly lower than that of individual series of fewer than 50 cases (Group 2) (χ^2 [1 *d. f.*] = 8.05, *P*, 0.005). Finally, the fetal mortality of all individual series combined (Groups 1+2) is significantly lower than collected series obtained by questionnaires (Group 3) (χ^2 [1 *d. f.*] = 40.21, *P* less than 0.001).

* When more than one report has appeared on the same group of patients they are classified as a single series.

† See footnote to Group 1.

TABLE 6.—*Comparison of Incidence of Stillbirths and Neonatal Deaths (Over Twenty-Eight Weeks' Gestation)*

	Preg., No.	Deaths: Intrauterine * No.	%	Neonatal † No.	%
1 (a). Individual series >50 cases (1 team)	1,508	134	8.4	180	11.9
1 (b). Individual series >50 cases (different physicians)	781	129	16.5	63	8.1
2. Individual series <50 cases	657	162	24.7	58	8.9
3. Collected series	1,226	344	27.4	119	9.7

* For intrauterine deaths: $\chi^2=152.2$; *d. f.*=3; $P=0.001$.
† For neonatal deaths: $\chi^2=9.56$; *d. f.*=3: $P=0.02$.

E. Stillbirths and Neonatal Deaths.—If deaths are separated into stillbirths and neonatal deaths, it becomes very apparent that the better result achieved by experienced teams is largely in the prevention of stillbirths. In Table 6 are listed all the data on cases where the relative proportion of stillbirths and neonatal deaths is known. It can be seen that the incidence of stillbirths rises from 8.4% in series controlled by single teams to 27.4% in the collected series. The differences are highly significant (χ^2 [3 *d. f.*]=152.2, P less than 0.001). On the other hand, the incidence of neonatal deaths in these two groups is 8.1% and 11.9%, a difference which is only of borderline significance (χ^2 [3 *d. f.*]= 9.56, $P=0.02$).

F. Changes in Mortality Rates.—Several investigators have attempted to show that the fetal mortality among infants of diabetic mothers has decreased in recent years.[3,73, 83,99,123,167,172,180,235] It therefore seemed worth while to compare the mortality figures of several of the larger groups from one period to another, as shown in Table 7. It is evident that in only one of the series was the difference significant, and that, in terms of rather small numbers of cases. This points to the need of exercising extreme caution in the interpretation of mortality statistics.

G. Summary.—Women with diabetes mellitus show a severalfold increase in the incidence of pregnancy failures as compared with normal women. Since infertility and miscarriages prior to the period of viability are not serious problems in such women, this excessive loss is limited exclusively to the period after the 28th week of gestation.

Comparison of mortality figures shows little to suggest a significant decrease in fetal mortality in recent years. Despite many enthusiastic claims to the contrary, no one group advocating a specific method of management has been able to achieve results which are significantly superior to those obtained by other clinics.

TABLE 7.—*Changes in Fetal Mortality Among Infants of Diabetic Mothers*

Authors	Series	Preg., No.	Fetal Deaths	%	χ^2 (*d. f.*)	*P*
Gellis & Hsia	1940-1950(a)	377	85	23	2.01 (1)	0.10-0.20
	1950(b)-1956	390	64	16.5		
Pedersen[177]	1946-1952	152	41	27	3.34 (1)	0.05-0.10
	1953-1955	113	17	15		
Long et al.[138]	1942-1948	62	22	36	2.96 (1)	0.10-0.20
	1948-1952	56	10	18		
Pedowitz & Shlevin[164]	1932-1949	141	31	22	8.55 (1)	0.005
	1950-1953	73	6	8		
Flowers & Levitt[73]	1936-1941	13	7	54		
	1941-1951	29	9	31	3.82 (2)	0.10-0.20
	1951-1953	20	3	15		
Pool & Oakley[183]	1944-1949	142	36	25		
					0.10 (1)	0.70-0.80
	1949-1956	183	51	28		

TABLE 8.—*Maternal Age and Fetal Mortality*

Authors	Age Groups, Yr.	Preg., Total No.	Deaths					
			Intra-uterine	Neo-natal	Total	%	x^2 (*d. f.*)	*P*
Gellis & Hsia	Less than 25	335	27	42	69	20		
	26-35	369	27	43	70	18	0.56 (2)	0.70-0.80
	Over 35	43	2	8	10	24		
Andersson[7]	Less than 30	27	--	--	13	48	0.69 (1)	0.30-0.50
	Over 30	29	--	--	13	35		

It would appear that specialized interest and experience in the problems of the pregnant diabetic is the one significant factor in reducing fetal mortality at the present time. The results achieved by a team of physicians caring for the mother and infant are significantly better than those achieved by changing medical personnel. Individual clinics handling more than 50 cases had better results than those with less experience. Reports from individual clinics showed a lower fetal mortality than questionnaire surveys. The differences between groups was most marked in reducing the number of stillbirths. Since this was accomplished without increasing the number of neonatal deaths, a greater number of pregnancies had a successful outcome.

IV. Maternal Factors

It is apparent that the fetus suffers greatly from the physiological disturbances associated with diabetes in the mother. These cause some of the infants to die while in utero and others to die shortly after birth. It is useful, therefore, to consider some of the individual maternal factors which might influence fetal mortality.

A. Maternal Age.—Information on the age of the mother during pregnancy is available in only two series of cases, as shown in Table 8. In neither was the difference in age significant. This would suggest that age per se should not be a contraindication for pregnancy in a woman with diabetes.

B. Parity.—A few years ago Andersson[7] expressed the opinion that primiparous women with diabetes tend to lose more of their babies than multiparous ones. More recent observations both by the Medical Research Council Study and in our own series failed to confirm this on a statistical basis (Table 9). In our group, the women with four or more pregnancies tend to do less well than the ones with fewer pregnancies. Although opinions vary regarding the size of family a diabetic woman should have, the present data would offer some support to Peel's[181] opinion that "the diabetic woman whose life is inevitably

TABLE 9.—*Parity and Fetal Mortality*

Authors	Parity	Preg., Total No.	Deaths					
			Intra-uterine	Neo-natal	Total	%	x^2 (*d. f.*)	*P*
Gellis & Hsia	1	353	20	40	60	17		
	2	219	20	24	44	19.5		
	3	117	7	13	20	17	8.80 (4)	0.05-0.10
	4	47	6	11	17	36		
	More than 4	31	3	5	8	26		
Andersson[7]	1	16	--	--	7	56	0.54 (1)	0.30-0.50
	More than 1	12	--	--	9	25		
Medical Research Council[188]	1	54	7	9	16	29	0.61 (1)	0.30-0.50
	More than 1	82	9	9	18	22		

TABLE 10.—*Past Obstetric History and Fetal Mortality* *

Past Obstetrical History	Preg., TotaNo.	Deaths					
		Intrauterine	Neonatal	Total	%	χ^2 (*d.f.*)	*P*
Miscarriages							
0	621	36	68	104	17.0		
1	168	13	16	29	27.5		
2	27	4	6	10	37.0	13.39 (3)	<0.01
3 or more	16	3	3	6	37.5		
Stillbirths							
0	715	49	87	136	19.0		
1	50	7	6	13	26.0	0.88 (1)	0.30–0.50
2	2	0	0	0	0		
Neonatal							
0	745	49	80	129	17.5		
1	75	7	11	18	24.0	6.85 (2)	0.02–0.05
2	4	0	2	2	50.0		

* Data of Gellis & Hsia.

modified and limited to some extent by her disease is seldom a suitable person to have a large family, apart from the deleterious effects of repeated pregnancies upon her diabetic condition and the fact that the diabetic patient is not the most suitable for reproduction from the genetic standpoint."

C. Past Obstetrical History.—Surprisingly, there is very little in the literature concerning the past obstetrical history of patients with diabetes mellitus. Turning again to Peel,[181] he states, "There is no doubt that there exists an entity we sometimes call a bad obstetrical history. . . . We find that approximately fifty per cent of our multiparous diabetics who lose their babies have already lost one or more previous pregnancies." Our own data presented in Table 10 suggest that women with previous miscarriages, stillbirths, and neonatal deaths tend to have a greater incidence of fetal deaths. This is not surprising, since subsequent fetuses are being subjected to the same unfavorable environment as the previous ones who succumbed. However, the past history is not as significant as in erythroblastosis fetalis, where a stillbirth or hydrops fetalis is very frequently followed by another. It is not an uncommon experience, for instance, for a diabetic woman to have a stillbirth, followed by a normal child, followed by a neonatal death, and followed yet by another normal child. An unfavorable obstetrical history, then, should not in itself discourage such women from trying again.

The catastrophe does not always take the same form. A woman with a previous stillbirth might have a neonatal death on a subsequent pregnancy, or vice versa. Ap-

TABLE 11.—*Duration of Maternal Diabetes and Fetal Mortality* *

	Gellis & Hsia		Long et al.[111]		Hurwitz & Higano[88]		Oakley[151]		Total No.	Total Deaths	%
	No.	Deaths	No.	Deaths	No.	Deaths	No.	Deaths			
Pregnancy only	11	0	35	12	53	6	--	--	99	18	18.0
0–5 Yr.	172	24	35	11	47	15	97	29	351	79	22.8
6–10 Yr.	236	52	33	7	25	6	72	20	366	87	23.7
11–19 Yr.	262	49	14	2	14	3	83	20	373	74	19.8
20 Yr. or longer	86	24	1	0	1	0	11	3	99	27	27.0

* $\chi^2 = 3.46$; $d.f. = 4$; $P = 0.50$.

parently, the unknown maternal factors leave their mark even if the infant is delivered alive.

D. Severity of Maternal Diabetes.—This may be defined in a number of different ways:

1. Duration: It is generally agreed that the duration of maternal disease has little to do with subsequent fetal mortality. In Table 11, the data are tabulated on the relationship between the duration of diabetes and fetal mortality in four of the largest series. The differences are not significant (χ^2 [4 *d. f.*]=3.46, P=0.50). This is not surprising in view of the strong evidence that prediabetic women also show a high fetal mortality.[141]

2. Age of Onset of Diabetes: Although investigators have often suggested that juvenile diabetics have greater difficulties with their pregnancies than women who develop the disease later in life, this does not appear to be the case. The published data of Oakley [101] and Long et al.[120] show no significant differences related to age of onset, as shown in Table 12.

TABLE 12.—*Age of Onset of Diabetes and Fetal Mortality*

	Preg., No.	Fetal Deaths	%	χ^2 (*d. f.*)	*P*
Oakley [101]					
1-15 yr.	70	21	30		
16-24 yr.	105	24	23	1.47 (2)	0.30-0.50
More than 25 yr.	92	29	31		
Long [120]					
1-22 yr.	17	4	23	0.11 (1)	0.70-0.80
More than 22 yr.	118	32	27		

3. Insulin Requirement: Similarly, Peel,[101] Oakley,[101] and Given et al.[68] have been unable to find any relationship between insulin requirement and fetal mortality. Hurwitz and Higano [96] share their feelings and divide the patients taking insulin into different degrees of severity. The differences in the three series are not significant (Table 13).

4. Classification of Severity: As early as 1933, Skipper [210] showed that pregnant women with severe diabetes suffered a 60%-70% fetal mortality, while those with moderate disease had a 40% loss, and those with mild disease, only a 30% loss. In order to demonstrate this effect, White, [246] in 1949, established an arbitrary system of classification based upon duration and severity of diabetes in the mothers as follows:

Class A. Abnormal glucose tolerance test only. No insulin required.

Class B. Onset of diabetes over the age of 20. Duration of diabetes, 0-9 years. No vascular changes.

TABLE 13.—*Insulin Requirement and Fetal Mortality*

	Preg., No.	Fetal Deaths	%	χ^2 (*d. f.*)	*P*
Hurwitz & Higano [96]					
Mild (no insulin)	45	4	9		
Moderate (1-20 units daily)	10	3	30		
Moderate severe (21-50 units daily)	22	9	40	7.3 (3)	0.05-0.10
Severe (51 units daily)	63	16	25		
Peel & Oakley, questionnaire series [101]					
Insulin	395	159	40	0.69 (1)	0.30-0.50
No insulin	42	14	33		
Given et al. [68]					
Insulin	78	20	25.5	0.18 (1)	0.70-0.80
No insulin	53	12	22.5		

Class C. Onset of diabetes between the ages of 10 and 20. Duration of diabetes, 10-19 years. No vascular changes.

Class D. Onset of diabetes under the age of 10. Duration of diabetes, more than 20 years. Vascular disease. Calcification in the legs, retinitis proliferans.

Class E. All of the above plus calcification of pelvic vessels.

Class F. Those with nephritis.

Although this method of classification is imperfect, no one has devised a better one. As a result, most authors have in recent years tabulated their data using this system of classification. This is fortunate because it makes comparison between series much easier.

Our own data, using White's system of classification, are tabulated in Table 14. The fetal mortality grows progressively worse as the degree of diabetes becomes severer

TABLE 14.—*Present Series According to Classification* *

Classification	Preg., Viable No.	Deaths: Intra-uterine	Deaths: Neo-natal	Deaths: Total	%
A	11	0	0	0	0
B	202	7	19	26	13
C	279	17	27	44	16
D	209	20	37	57	27
E	35	9	1	10	29
F	31	3	9	12	39
Total	767	56	93	149	19.5

* χ^2=20.5; *d. f.*=4; P<0.01.

TABLE 15.—*Other Series According to Classification* *

Classification	Adams		Pedowitz		Pedersen		Long		Total	
	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths
A	3	0	2	0	--	--	0	0	5	0
B	38	6	44	2	85	20	89	18	256	46
C	34	5	24	1	72	11	23	5	153	22
D	24	5	3	0	87	22	23	6	137	33
E	0	0	0	0	--	--	0	0	0	0
F	2	0	0	0	--	--	3	3	5	3

* $\chi^2 = 8.1$; *d. f.* = 3; $P = 0.02$-0.05.

(χ^2 [4 *d. f.*] = 70.5, P less than 0.01). The experiences of Adams,[3] Pedowitz,[180] Pedersen and Shlevin,[177] and Long et al.[123] are tabulated in a similar fashion in Table 15. Here there are fewer cases of Classes E and F for comparison, but the differences are still suggestive (χ^2 [3 *d. f.*] = 8.1, P = 0.02-0.05). It is of interest to note that most of the fetal deaths among women with calcified pelvic arteries occurred in utero, while the deaths among those with nephritis occurred after birth. This may serve as an important clue to the mechanism for fetal deaths in these pregnancies.

During the past few years, we have had an unusual opportunity to observe a number of diabetic pregnancies in women with nephritis.[164] In these women, all of the physiological problems of the pregnant diabetic are exaggerated to the ultimate degree. The women have more than the usual degree of toxemia and hydramnios and frequently have to be delivered early because of medical indications. Many of the infants are actually smaller than premature infants who are of the same gestational age born of nondiabetic women. Even when delivered very prematurely, the placenta appears postmature with calcification of the vessels. Oxygen tension has been measured in the umbilical vein at delivery, and some readings have been among the lowest ever recorded. The fetus shows little growth in the uterus after the 32d week, and the chances of its dying become progressively greater. Regardless of the time of delivery, the majority show marked respiratory distress and nearly half die in the neonatal period. Hyaline membranes are usually the only findings at postmortem examination. Although proof is lacking, it would appear that throughout pregnancy the fetus has been suffering from inadequate circulation from the mother and the clinical picture represents the end-result of prolonged anoxia.

E. Control of Diabetes During Pregnancy.—Without question, good control of maternal diabetes is essential for successful outcome of a diabetic pregnancy. As early as 1931, Peckham [173] pointed out the relationship between poor diabetic control and fetal death in utero. Given, Douglas, and Tolstoi [83] found that 7 out of 12 patients whose infants died and who had no evidence of toxemia had bouts of ketoacidosis and

TABLE 16.—*Control of Maternal Diabetes and Fetal Mortality*

Degree of Control	Preg., Total No.	Fetal Deaths	%	χ^2 (*d.f.*)	*P*
Skipper, collected series [110]					
Good	60	10	16.6		
Moderate	41	28	68.2	24.0 (2)	<0.005
Poor	20	18	90.0		
Skipper, own series [110]					
Good	20	3	15		
Moderate	15	10	66.6	7.56 (2)	0.02-0.05
Poor	2	2	100		
Lawrence & Oakley [119]					
Complete superior	32	11	28		
Partial superior	4	2	50	2.82 (2)	0.20-0.30
None	10	7	70		
Pedersen & Brandstrup [177]					
Long-term case	130	13	10	14.3 (1)	<0.005
Short-term case	135	45	31		

TABLE 17.—*Toxemia and Fetal Mortality* *

	Toxemia			Nontoxemia		
	Preg., Total No.	Fetal Deaths	%	Preg., Total No.	Fetal Deaths	%
Peel & Oakley, Q series [183]	86	38	44.2	360	145	40
Peel & Oakley, U C H [183]	15	7	46.7	126	29	23.0
Hurwitz & Higano [93]	40	12	30	100	20	20
Given, Douglas, & Tolstoi [93]	60	17	28.5	71	9	12.5
Hall & Tillman [93]	34	8	24	73	14	19
Total	235	82	35	730	217	29.5

* $\chi^2 = 1.14$; $d.f. = 1$; $P = 0.20$-0.30.

insulin reactions during the antenatal course. White [246] goes so far as to state that only two infants in her series had survived a bout of diabetic coma in the mother and that poor control of maternal diabetes accounts for 5% of all fetal fatalities, most of these occurring in utero.

The data on diabetic control and fetal mortality are tabulated in Table 16. In each instance, the fetal mortality in the poorly controlled group is greater than in the well-controlled group. In this era, good control of maternal diabetes can be accomplished in almost every patient. Since control of diabetes appears to be one of the few factors that significantly alters fetal mortality, every physician caring for a pregnant woman with diabetes should regard good control as his first and most important objective.

F. Toxemia and Hydramnios.—Early observers were impressed not only by the frequency with which preeclamptic toxemia developed in the last trimester of diabetic pregnancy but also by the frequency with which its appearance is attended or followed by intrauterine death of the fetus. There appears to be little doubt that the incidence of toxemia is increased, and it has been given as 33% by Tew,[232] 43% by Barns and Morgans,[13] 10% by Lawrence and Oakley,[118] and 36% by White.[245] However, there is no general agreement that the appearance of toxemia is necessarily a bad sign. In Table 17 are given the differences in fetal mortality in women with and without toxemia from four of the larger series. The differences are not significant (χ^2 [1 $d.f.$] = 1.14, P = 0.20-0.30).

Similarly, there is no strong reason to believe that hydramnios itself will markedly affect the outcome. With use of Peel and Oakley's [182] own data, the differences between the women with and without hydramnios are not significant (χ^2 [1 $d.f.$] = 2.87, P = 0.05-0.10) (Table 18).

We have not presented any of our own data because we find it extremely difficult to judge these factors. Certainly, almost every woman with diabetes develops excessive hydramnios and a fair number show evidences of preeclampsia in the latter part of pregnancy. This cannot always be controlled by the low-salt diet, diuretics, ammonium chloride, etc. Amniotomies have occasionally been performed; however, differences between such women are largely a matter of degree, and at this point satisfactory methods have yet to be devised to measure such changes objectively. Clinically, we have been unimpressed by the ef-

TABLE 18.—*Hydramnios and Fetal Mortality* *

	Hydramnios		No Hydramnios	
	Preg., Total	Fetal Deaths	Preg., Total	Fetal Deaths
Peel & Oakley				
Q series [183]	122	56	336	127
UCH [183]	43	19	96	17
Total	165	75 (45%)	434	144 (33%)

* $\chi^2 = 2.87$; $d.f. = 1$; $P = 0.05$-0.10.

fect of these factors upon ultimate outcome. There were 11 fetal deaths among 89 pregnancies where hydramnios appeared particularly marked, an incidence of 12.5%, which does not differ markedly from the over-all mortality rate. However, since it appears that hydramnios and toxemia are deleterious for the fetus, they should be prevented if at all possible.

G. The Role of Hormones.—1. Physiological Changes in Diabetic Pregnancies: Workers in this field have always been intrigued with the possibility of repeating the physiological changes in animals. In 1947 Miller [137] produced diabetes mellitus in female animals of various species by injecting alloxan. He found that when such rabbits became pregnant many abortions, premature deliveries, stillbirths, and immature fetuses resulted. However, he was unable to demonstrate these changes among diabetic rats and dogs.

Barns et al.[12] repeated these experiments using rats and found that there were 27 stillbirths and 24 neonatal deaths in 153 pregnancies, or a total mortality of 37% among offspring of rats with alloxan diabetes. Fetal resorption occurred in three instances. Also, only 50% of the live-born rats survived after the weaning period. When crude anterior pituitary extract (APE) was given, the stillbirth rate was increased to 100%. Engfeldt and Hultquist,[63] working independently in Sweden, noted the same finding and felt that the changes in the endocrine glands of fetuses closely resembled, both qualitatively and quantitatively, those demonstrated in the newborn giant young of female rats with diabetes resulting from excision of the pancreas.[97] They both felt that an overproduction of diabetogenic growth complex by the maternal anterior pituitary may be responsible for the high late fetal mortality rate in diabetic and prediabetic women.

Unfortunately, subsequent studies have clearly demonstrated that this is not the sole factor. Barns and Swyer [15] reported their experiments using pure APE in non-diabetic pregnant animals and were unable to find a significant difference in fetal weight of the treated and control groups. Similarly, Engfeldt and Hultquist,[63] using a crystalline growth hormone, were unable to demonstrate in the same degree changes in birth weights, mortality rates, and endocrine organs in the offspring of pregnant rats as with the crude preparation. This, together with the recent observation of Abelove et al.[1] on the offspring of acromegalic mothers, does not offer much support for the theory of overproduction of growth hormone in diabetic women.

Turning to direct physiological observations, the first suggestion of a possible hormonal imbalance in diabetic pregnancies was made in 1933, by Murphy,[155] who reported that the prolan excretion in two diabetic women exceeded the normal range. This work was carried further by Smith and Smith [211,212,214,223] who, in evaluating the problems of hormones in preeclamptic toxemia, very naturally turned to the problems of levels in pregnant women with diabetes where the incidence of toxemia was known to be great. In their earlier investigations, they showed that there was an excessive chorionic gonadotropin and low levels of estrogen in the serum and urine of patients exhibiting toxemia and eclampsia. Later, the abnormal rise in serum chorionic gonadotropin was found to precede clinical signs by some weeks.

This abnormal hormonal pattern in pregnant women with diabetes has been repeatedly confirmed.[106,124,133,201,223,248-250] By 1943, White [244] was able to report on hormone assays for chorionic gonadotropin and pregnanediol in 125 consecutive cases. The pattern was classified as normal in 41 cases. Of these, nine delivered prematurely, 2% developed toxemia, and 95% of the fetuses survived. The pattern was abnormal in 27 cases who received no substitutional hormone therapy. Of these, 52% developed toxemia, 40% were delivered prematurely, and only 60% of the fetuses survived. More recently, the Medical Research Council undertook a controlled study on the role

of steroids in preventing fetal mortality in women with diabetes.[133] Although they were unable to demonstrate any benefit from oral diethylstilbestrol and ethisterone therapy, there was evidence of significant differences during the few weeks before delivery between the urinary output of pregnanediol-like substances in pregnancies ending in stillbirths or neonatal death and in the successful pregnancies. The level of the pregnanediol-like substances tended to rise after the eight-month period in successful pregnancies but fell in those ending in stillbirth or neonatal death. In the same way, the urinary chorionic gonadotropin levels in unsuccessful pregnancies tended to fall in the last month. This ominous pattern of declining output of the substance assayed occurred in unsuccessful pregnancies in both the hormone-treated patients and the non-hormone-treated controls.

2. Their Use in Nondiabetic Pregnancies: In 1938, Smith and Smith [213] proposed that since there were low levels of estrogen and high levels of anterior pituitary-like substances in the serum and urine of patients with toxemia, estrogens should be given to reestablish a balance between the two. Later, this was also recommended as a means of preventing late accidents in pregnancy.[217,218] Much of this work was based on the suggestion that such accidents are related to a deficiency in the secretion of progesterone and other sex steroids by the placenta and that the secretion of these steroids can be stimulated with diethylstilbestrol. This work became open to question when Davis and Fugo [49,50] failed to demonstrate a rise of urinary pregnanediol when diethylstilbestrol was administered and showed that the rise was due to lack of specificity of the method for assay. This has subsequently been confirmed by studies on endogenous estrogen metabolism.[171,227] The subsequent publications by Dr. Olive Smith [220,221,225] are difficult to interpret in the light of these findings.

The clinical results with diethylstilbestrol therapy are not impressive. Gitman and Koplowitz [82] and the Smiths,[215,219,224,225] who favor the use of sex hormones, do not have data which are properly controlled. However, even using comparative data, the two larger series presented by the Smiths are probably not statistically significant (Table 19). On the other hand, Ferguson [69] and Dieckmann et al.[54] have undertaken controlled studies and their data show no difference between the diethylstilbestrol-treated patients and the controls (Table 19).

3. Their Use in Diabetic Pregnancies: The use of female sex hormones in the correction of hormonal imbalance in diabetic pregnancies has been the subject of intense study for the past 15 years. As early as 1939, White and her co-workers [250] showed

TABLE 19.—*Comparison of Diethylstilbestrol- and Non-Diethylstilbestrol-Treated Pregnancies in Nondiabetic Women*

Authors	Cases, No.	Deaths			χ^2 (d. f.)	P
		Stillbirths	Neonatal	Total		
Smith & Smith [215]						
Diethylstilbestrol-treated	387 *	2	6	8	2.63 (2)	0.10-0.20
No treatment	555 *	2	15	17		
Smith & Smith [219]						
Diethylstilbestrol-treated	168 †	--	--	10	4.39 (1)	0.02-0.05
B. L.-I. vital statistics	1,492 †	--	--	167		
Ferguson [69]						
Diethylstilbestrol-treated	190	3	4	7	0.88 (1)	0.30-0.50
Placebo	200	4	7	11		
Dieckmann et al. [54]						
Diethylstilbestrol-treated	840	7	16	23	3.90 (1)	0.02-0.05
Placebo	806	8	4	12		

* Primigravida only.
† Infants weighting less than 2500 gm.

that such women had high serum prolan levels and that replacement therapy with estrin and progesterone (Progestin) resulted in the restoration of serum prolan to normal levels and the successful outcome of the pregnancy. In 1949, she published the dosage of diethylstilbestrol and proluton on the basis of severity of diabetes by classification.[245] She reported that in 47 cases with a normal hormonal balance, the fetal survival rate was 95%; in 297 cases with corrected hormonal imbalance, the fetal survival rate was 89%, and in 89 cases in which the hormonal imbalance was uncorrected, the fetal survival rate was only 58%.

Unfortunately, there is little in the literature that can be compared with White's extensive series. Loraine,[124] in measuring the excretion of chorionic gonadotropin in pregnant diabetics, found that the excessively high levels were corrected by the administration of estrogens. Keltz, Keaty, and Hellbaum [105] were unable to alter either the blood chorionic gonadotropin or the urinary pregnanediol excretion with diethylstilbestrol and progesterone (Proluton) therapy. Finally, the Medical Research Council Study [133] concluded that there was some evidence to suggest a significantly higher output of pregnanediol-like substances in the hormone-treated patients, but this had no effect on the pattern of hormone secretion associated with fetal loss described above.

Results from the clinical use of female sex hormones in diabetic pregnancies are equally inconclusive. In 1954, the Medical Research Council [133] undertook a controlled study to determine the therapeutic value of oral diethylstilbestrol and ethisterone therapy. There were 17 deaths among the 70 viable pregnancies receiving hormone treatment and 17 deaths among the 66 viable pregnancies receiving a placebo. It would be improper for us to enter this controversy, since the vast majority of the patients in our own series received full hormonal therapy. Instead, we can tabulate our findings together with those of the other more recent series of more than 100 cases, as shown in Table 20. The differences in fetal mortality between the two groups are not statistically significant (χ^2 [1 *d. f.*] = 3.59, P = 0.05-0.10).

TABLE 20.—*Comparison of Hormone- and Non-Hormone-Treated Pregnancies in Diabetic Women* *

Authors	Hormones		No Hormones	
	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths
Hsia & Gellis	312	68	103	33
Pedersen & Brandstrup [177]	—	—	265	58
Jones [100]	21	6	183	51
Tolstoi et al. [224]	—	—	182	48
Long et al. [103]	—	—	118	32
Adams [2]	—	—	101	16
Medical Research Council [133]	70	17	66	17
Peel & Oakley [151]	56	21	—	—
Smith & Smith [214]	42	7	72	17
Total	701	144	1,090	272

* χ^2=3.59; *d. f.*=1; P=0.05-0.10

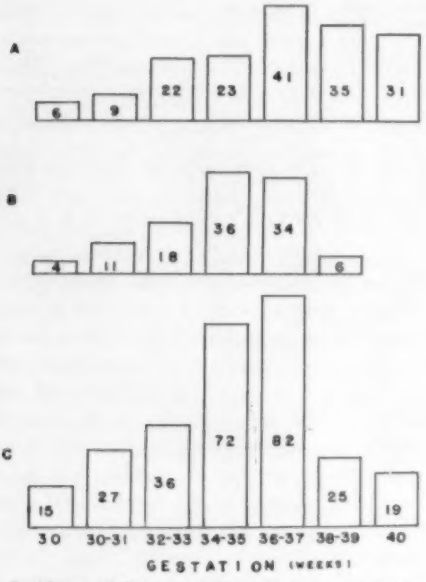
H. Summary.—Only two maternal factors appear to influence the fetal mortality of diabetic pregnancies: (1) severity of maternal disease as measured by White's classification, which emphasizes long-term effects of diabetes, such as calcification of the pelvic vessels and nephritis in the mother, rather than age of onset or duration alone, and (2) prevention of acidosis and good control of diabetes in the mother. All other factors, such as maternal age, parity, past obstetrical history, insulin requirement, toxemia, and hydramnios, are probably of less or of no importance.

While there is good evidence that diabetic women suffer from a hormonal inbalance during pregnancy and that this frequently is associated with death of the fetus, there is at present no clear-cut evidence to suggest that substitution therapy with femal sex hormones either completely corrects the defect or significantly reduces the fetal mortality rate.

V. Obstetrical Factors

It is generally agreed that the risk of intrauterine death of the fetus in diabetic pregnancies rises gradually from the 32d to the 40th week and that after the 36th week

stillbirths frequently exceed neonatal deaths. It is also generally agreed that labor may be poor in the diabetic, that the fetus of a diabetic woman withstands the normal buffetings of labor and vaginal delivery poorly, and that a certain proportion of such infants are lost in the course of passage through the birth canal. Despite this, there appears to remain a considerable controversy as to the optimal time and mode of delivery for such infants. The present review will attempt to present the facts as they appear in the literature.



Incidence of fetal mortality based upon gestation (weeks). *A*, number of stillbirths, based upon the data of Gellis & Hsia, Adams,[8] Reis et al.,[100] Anderson,[6] and Peel & Oakley.[103] *B*, number of neonatal deaths, based upon the data of Gellis & Hsia, Adams,[8] Reis et al.,[100] and Anderson.[6] *C*, total fetal mortality, based upon the data of Gellis & Hsia, Adams,[8] Reis et al.,[100] Anderson,[6] Pedowitz & Shlevin,[102] Cardell,[99] and Hurwitz & Higano.[98]

A. Optimal Time of Delivery.—It is pertinent to examine first the question of when most infants of diabetic mothers die. In the Figure this information based upon figures available from several of the large series is plotted. It can be seen that the total number of stillbirths increases steadily from the 30th week on and reaches a peak at 36-37 weeks of gestation. However, despite the fact that few infants of diabetic mothers are delivered after the 38th week, the total number of stillbirths remains high right up to term. Over one-third of all the infants delivered after the 38th week are stillborn. In contrast, the total number of neonatal deaths reaches a peak at 34-37 weeks and is negligible thereafter. The additive effects of the two factors are given in the lower portion of the chart.

In the final analysis, the only important factor is the proportion of babies discharged home alive and well. Therefore, fetal mortality is only meaningful when expressed as percentage of total pregnancies during each of the gestation periods, as shown in Table 21. It is obvious that the 35- to 36-week period is the optimal time for delivery, since only 11% of the infants delivered at this time died and this rate is not a great deal higher than among infants of normal women. The death rate in the 33- to 34-week period is somewhat poorer. However, if the infants are delivered prior to the 32d week more than half will die because of prematurity, and after the 37th week more than one-quarter will be stillborn.

TABLE 21.—*Incidence of Fetal Mortality Based on Length of Gestation*

	Gellis & Hsia		Adams[8]		Reis et al.[100]		Andersson[7]		Total		
Gestation, Wk.	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	Preg., No.	Fetal Deaths	%
28-32	58	35	6	3	3	2	3	4	70	44	63
32-34	154	27	7	0	3	1	7	4	171	32	19
35-36	429	47	39	5	10	0	14	1	492	53	11
37-40	126	40	49	8	40	4	18	9	233	61	26
—	—	—	—	—	—	—	—	—	—	—	—
Total	767	149	101	16	56	7	32	18	800	190	22

Unfortunately, the obstetrician does not always have the final decision as to the date of delivery. A number of women go into spontaneous labor prior to the 33d week. Others require emergency delivery or cesarean section because of poor control of diabetes, increasing hydramnios and fluid retention, decrease of fetal movements or loss of fetal heart sounds, or the development of a so-called "halo" sign indicating increasing edema of the fetus. It is because of these unpredictable situations that White [246] and Pedersen and Brandstrup [177] advocate constant observation in the hospital for several weeks prior to the date of delivery. It is probably this factor which largely accounts for a decrease in the absolute number of stillbirths among the cases managed by a team.

B. Mode of Delivery.—Opinions vary widely on this most important question. Some reports are enthusiastic about delivery by cesarean section [123,159,180,190]; others cautiously recommend it,[7,83,152,195] and others [88, 134,177] feel that the procedure should be reserved only for obstetrical indications and claim equally good results under such circumstances. Certainly, the good results in a large series of cases reported by Pedersen and Brandstrup [177] emphasize that cesarean section is not the decisive factor in lowering fetal mortality.

TABLE 22.—*Neonatal Deaths as Related to Mode of Delivery* *

	Cesarean Section		Pelvic Delivery	
	Preg., No.	Neonatal Deaths	Preg., No.	Neonatal Deaths
Gellis & Hsia	510	59	201	34
Peel & Oakley, [191]				
Q series	112	51	209	35
UCH series	98	16	27	4
Randall [190]	26	1	18	3
Pedowitz & Shlevin [190]	45	1	34	1
Reis et al. [190]	34	1	21	1
Andersson [7]	10	1	25	8
Total	835	94 (11%)	535	86 (16.2%)

* χ^2=5.21; *d. f.*=1; *P*=0.02-0.05.

TABLE 23.—*Incidence of Respiratory Distress Depending upon Mode of Delivery* *

Mode of Delivery	Preg., No.	Resp. Distress	%
Cesarean section	510	160	31.5
Pelvic delivery	201	72	35.5
Total	711	235	32.5

* χ^2=0.355; *d. f.*=1; *P*=0.50-0.70.

It is impossible to compare the results of vaginal delivery with those of cesarean section because all of the fetuses dead in utero are usually delivered vaginally. Therefore, in Table 22 we have excluded all stillbirths and included only the infants who were born alive of diabetic mothers. It can be seen that the neonatal mortality among those delivered by cesarean section was 11.0%, while that among those delivered vaginally was 16.2%. The difference is possibly significant (χ^2 [1 *d. f.*] = 5.21, *P* = 0.02-0.05).

It should be remembered, however, that most of the diabetic women who go into spontaneous labor prior to the 33d week are delivered vaginally. If one excludes all deliveries both by cesarean section and by the pelvic route prior to the 33d week, one may better evaluate fetal risk by both methods. Using our own data, we found that 53 infants out of 493 women delivered by cesarean section died during the neonatal period, a mortality rate of 10.7%. In the same period, 23 infants out of 168 women delivered vaginally died during the neonatal period, a mortality rate of 13.7%. The difference is now no longer significant (χ^2 [1 *d. f.*] = 1.17, *P* = 0.20-0.30).

Perhaps most striking is the failure of cesarean section to affect the incidence of respiratory distress among these infants. It is well known that a large proportion of infants of diabetic mothers suffer from the hyaline-membrane syndrome, and it has been suggested that cesarean section might contribute to its increased incidence.[30,99] With use of the criteria for grading the disease which will be discussed subsequently, it was found that the infants delivered by cesarean section did not show more respiratory dis-

TABLE 24.—*Comparison of Neonatal Deaths as Related to the Mode of Labor* *

	Spontaneous Labor		Induced Labor	
	Preg., No.	Neonatal Deaths	Preg., No.	Neonatal Deaths
Gellis & Hsia	132	20	60	8
Peel & Oakley [181]	111	24	91	15
Total	243	50	160	23 (14.5%)

* χ^2=0.63; *d. f.*=1; *P*=0.30-0.50.

tress than those delivered vaginally (Table 23). The difference is not significant statistically (χ^2 [1 *d. f.*]=0.355, *P*=0.50-0.70).

C. Induction of Labor.—If a patient is to be delivered by the vaginal route, it is important to determine if the risk of induced labor is greater than that of spontaneous labor. Our own experiences, together with those of Peel and Oakley,[182] are tabulated in Table 24. The neonatal mortality for those delivered by spontaneous labor appears slightly higher than for those delivered after induction, although the differences are not significant (χ^2 [1 *d. f.*]=0.63, *P*=0.30-0.50).

If one corrects for the spontaneous deliveries prior to the 33d week of gestation, however, this difference is even less marked. In our own group of patients, there were 104 patients who were delivered after spontaneous labor, with 11 neonatal deaths, a mortality of 10.5%. In comparison, there were 6 neonatal deaths among 64 patients who were induced after the 33d week, a mortality of 9.5%.

D. Anesthesia.—Useful information on the type of anesthesia employed in delivery from Peel and Oakley [182] and our own series is tabulated in Table 25. It is apparent that no great differences exist between the use of general and spinal-caudal type of anesthesia (χ^2 [1 *d. f.*]=0.508, *P*=0.30-0.50). The somewhat higher incidence of neonatal deaths after local anesthesia only indicates that it is probably chosen for the severest and most desperate cases, in which one would expect a higher fetal mortality. However, the differences are still not significant (χ^2 [1 *d. f.*]=2.87, *P*=0.10-0.20). In our own clinic, we generally have women inhale oxygen during delivery by cesarean section. Although there is no scientific evidence that this alters the outcome, it may be helpful in view of the hypoxia of newborn infants of mothers with diabetes.[246] Further study will be needed to determine its value, if any.

E. Summary.—Given a choice, infants of diabetic mothers should ideally be delivered between the 35th and 36th week of gestation. The neonatal mortality rate is excessively high prior to the 33d week, and early delivery should, therefore, be avoided if possible. Even more important, there is no evidence that spontaneous labor should be awaited after the 37th week, for during this period one out of three infants is stillborn.

There is no very clear evidence that the mode of delivery and type of anesthesia play a decisive role in fetal mortality. It is probably wise to pursue a policy of flexibility. Patients should be hospitalized and carefully followed for several weeks prior to term. Although an ideal date for delivery might be fixed, there is no contraindication for changing plans should fetal

TABLE 25.—*Neonatal Deaths and Type of Anesthesia Used During Delivery* *

	Peel & Oakley [181]		Gellis & Hsia		Total	
	Preg., No.	Deaths	Preg., No.	Deaths	Preg., No.	Deaths
1. General	95	18	16	3	111	21 (19%)
2. Spinal or caudal	59	9	347	53	406	62 (15%)
3. Local	33	5	13	7	46	12 (26%)

* Comparison of 1 and 2 gives rise to χ^2 of 0.51 and comparison of 2 and 3 gives rise to χ^2 of 2.87, each with 1 *d. f.* In both instances, p more than 0.05.

TABLE 26.—*Fetal Mortality of Normal and Diabetic Infants Divided According to Sex*

	Males			Females			
	Preg., No.	Deaths	%	Preg., No.	Deaths	%	Mortality (M/F)
General population (Crosse)							
Stillbirths	10,806	254	2.35	9,533	195	2.05	1.114
Neonatal deaths (all infants)	10,552	329	3.12	9,338	202	2.81	1.111
Neonatal deaths (premature)	629	115	18.3	748	92	12.3	1.487
Infants of diabetic mothers (Gellis & Hsia)							
Stillbirths	366	24	6.55	379	10	2.63	2.490
Neonatal deaths	342	53	15.5	369	40	10.8	1.435

movement decrease, fetal heart rate alter, or a "halo" sign appear, at which point the infant should be delivered by cesarean section in the attempt to prevent stillbirth. Similarly, there is no reason why many of the patients should not be induced and delivered vaginally if the cervix is favorable, but cesarean section should be performed at the first indication of obstetrical difficulty.

VI. Pediatric Factors

Up to this point, we have been able to draw upon the large amount of statistical information available in the literature. Now, we must of necessity turn to our own experiences in the clinical management of some 722 infants born alive of diabetic mothers. This will be done by first taking up such general factors as sex, size, maturity, and condition of the infant at birth to evaluate their role in prognosis. We shall then describe the clinical course of such infants and review some of the laboratory data which have been obtained. Finally, we shall summarize the postmortem examination findings in the 104 infants who failed to survive.

A. General Considerations.—1. Sex: There is universal agreement that among normal infants at the age of viability there are more boys than girls. However, the proportions tend to equalize, because fewer boys survive. This is shown very clearly by the Birmingham data of Crosse,[48] which are tabulated in Table 26. It can be seen that the mortality rate of boys is approximately 10% greater in utero and again in the neonatal period. The latter figure increases to about 50% when only premature infants are considered.

This disproportionate sex ratio appears to be even more marked among infants of diabetic mothers. In our own experience, there were almost one and one-half times more stillbirths among boys as compared with girls. Similarly, there was a 43% increase in neonatal deaths in boys over girls.

In Table 27, the proportions of boys and girls reaching viability and ultimately surviving are compared. It can be seen that although the mortality rate is higher among boys than girls in normal infants, the ratio between boys and girls is altered only very slightly. On the other hand, among the diabetic infants there are slightly fewer boys to start with and by the time the infants are discharged from the hospital there are nearly seven more girls than boys

TABLE 27.—*Proportion of Males and Females Conceived and Surviving Neonatal Period*

	Normal Infants				Diabetic Infants			
	Males		Females		Males		Females	
	No.	%	No.	%	No.	%	No.	%
Total births	10,806	53.1	9,533	46.9	366	49.1	379	50.9
Born alive	10,552	53.0	9,388	47.0	342	48.1	369	51.9
Survived neonatal period	10,223	52.9	9,076	47.1	289	46.7	329	53.3

in each 100 infants. One might speculate as to whether the ratio of boys to girls among diabetic pregnancies was essentially the same as in the normal population at conception, but the male survival is so poor that a slightly abnormal ratio exists by the time the infant reaches the age of viability and this becomes marked by the end of the neonatal period.

2. Birth Weight: We [95] have presented a detailed analysis of birth weight in infants of diabetic mothers. We show that their weights are essentially the same as those of normal infants up to the 28th week of gestation. The birth weights then increase much more rapidly than among normal infants, so that by term they weigh between ½ to 1 lb. more (Table 28). However, it was

TABLE 28.—*Mean Birth Weight for Given Gestation Time* *

Gestation Time, Days	Birth Weight, (Lb.) Untreated	Treated
219	3.22 (1)	4.00 (2)
237	5.72 (4)	5.05 (20)
252	7.17 (44)	6.64 (213)
267	7.73 (44)	7.12 (228)
282	8.30 (9)	6.98 (29)
297	7.27 (3)	9.00 (1)
All	7.39 (105)	6.79 (499)

* The infants born of mothers treated with sex hormones during pregnancy are compared. The size of each group is given in parentheses.

noted that the infants born of mothers treated with female sex hormones during pregnancy did not show this change and had birth weights which were essentially similar to those of normal infants (Table 28). One wonders if the so-called "diabetogenic growth" hormone of the anterior pituitary postulated by Barns [11] and Gilbert and Dunlop [79] might in some way be suppressed by steroid therapy.

The fetal mortality rate based upon weight at birth is presented in Table 29. It would appear that 6-8 lb. is the optimal weight range for delivery, when the death rate is only moderately higher than in normal infants. The fetal mortality progressively increases with decreasing birth weight, and an infant (of a diabetic mother) weighing 3-4 lb. or 4-5 lb. has a much poorer expectation of survival than a normal infant with the same birth weight. It is also noteworthy that the fetal mortality increases in the heavier weight groups, largely because of stillbirths.

TABLE 29.—*Fetal Mortality Based upon Birth Weight*

Birth Weight, Lb.	Viable Preg., No.	Deaths Intra-uterine	Deaths Neo-natal	Deaths Total	%
3	14	10	4	14	100
3-4	24	3	15	18	75
4-5	64	8	17	25	39
5-6	154	5	18	23	15
6-7	198	3	14	17	9.0
7-8	178	5	10	15	8.5
8-+	119	11	5	16	13.5
Unknown	11	11	0	11	100.0
Total	767	56	93	149	19.5

In the same study, we also noted that the birth weight in infants of diabetic mothers decreased as the maternal diabetes became severer and of longer duration (Table 30). This may be due in part to a decrease in blood supply and oxygen to the placenta as a result of increased arteriosclerotic changes in the mother. Berglund and Zetterstrom [23] and Sutherland and his co-workers [231] have shown a decrease of oxygen saturation in the cord blood of such infants at delivery.

Cardell [39] has shown that infants of diabetic mothers lose 8.9% of their body weight

TABLE 30.—*Mean Birth Weight Based upon Severity of Maternal Diabetes* *

Classification	Birth Weight † Untreated	Treated
A	6.96 (6)	7.03 (4)
B	7.72 (52)	7.08 (141)
C	7.16 (34)	6.85 (194)
D	6.97 (12)	6.73 (125)
E	—	6.02 (21)
F	8.88 (1)	5.35 (14)
All	7.39 (105)	6.79 (499)

* Based on the classification of White. [210]
† The size of each group is given in parentheses.

TABLE 31.—*Weight Loss Expressed as Percentage of Birth Weight in Infants of Diabetic Mothers*

Day	Weight Loss, %
2	6.9
3	8.1
4	8.2
5	8.6
6	8.0
7	6.9
Maximum	9.6

during the early neonatal period, as compared with 5.7% in normal infants. The data on initial weight loss in 130 of the infants in our series are summarized in Table 31. They essentially confirm the earlier observations of Cardell. However, we have been unable to demonstrate any correlation between weight loss and respiratory distress (Table 32).

3. Length of Gestation: This has already been discussed in the previous section (Table 21 and Figure). It is important to emphasize once again that early delivery prior to the 33d week of gestation usually results in the loss of the infant and should not be undertaken except as a lifesaving procedure for the mother.

4. Condition at Birth: Apgar [8] has recommended a method for evaluating newborn infants immediately after delivery (Table 33). The infants in the present series were rated with use of these criteria, and it can be seen that some correlation exists between condition of infants at birth and subsequent clinical outcome ($\chi^2 = 55.0$ [3 *d. f.*], $P =$ less than 0.01 (Table 34).

TABLE 33.—*Evaluation of the Newborn Infant, Method of Scoring* * *

Sign	0	1	2
Heart rate	Absent	Slow (below 100)	Over 100
Respiratory effort	Absent	Slow, irregular	Good—crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

* Sixty seconds after the *complete* birth of the infant (disregarding the cord and placenta) these 5 objective signs are evaluated and each given a score of 0, 1, or 2. A score of 10 indicates an infant in the best possible condition.

TABLE 32.—*Comparison of Percentage Weight Loss in Infants with Respiratory Distress and Those with No Distress*

Day	Weight Loss, %	
	Respiratory Distress	No Distress
2	8.2	7.4
3	9.1	7.8
4	9.1	7.9
5	11.2	7.8
6	9.7	7.4
7	9.5	6.9
Maximum	10.9	9.2

B. Clinical Course.—Clinically, the infant of a diabetic mother may show no abnormal signs and have a completely normal course or may exhibit respiratory distress immediately after birth. Frequently, the signs of respiratory distress may be present but minimal at birth and become striking in their manifestations within a few hours after delivery. The signs consist of increased respiratory rate, with or without cyanosis, together with retraction of the soft tissues of the chest wall and a constant complaining cry. Examination reveals poor aeration of the lungs and inspiratory rales which are inconsistent but heard throughout the lung fields. X-ray reveals a fine type of atelectasis throughout the lungs. The respiratory distress becomes increasingly severe over the next hours of life, and the

TABLE 34.—*Fetal Mortality Based upon Condition of Infant at Birth*

Score	Viable Preg., No.	Neonatal Deaths	%
10	571	56	10
7-9	73	10	13
4-6	36	10	28
0-3	29	17	58
Total	711	93	12

TABLE 35.—*Clinical Signs of Respiratory Symptoms in Infants of Diabetic Mothers*

	No.	%
I. Total viable infants	711	
Infants with respiratory distress clinically	216	30.5
II. Time of onset of respiratory symptoms		
0-6 hr.	175	81.0
6-24 hr.	14	6.5
24 or more hr.	12	5.5
Not recorded	15	7.0
III. Duration of respiratory symptoms		
0-24 hr.	85	39.0
24-48 hr.	79	36.5
48 or more hr.	25	11.5
Not recorded	27	12.5
IV. Type of respiratory symptoms		
Hoarseness & cough	195	90
Complaining cry	193	89
Retraction of chest wall	178	81
Cyanosis	119	55

infant dies of respiratory failure after 24-72 hours or very gradually begins to improve and recovers completely over the same period of time.

Respiratory distress is the single most important finding in the infant of the diabetic mother,[43,76,77,86] and other factors, such as hypoglycemia, congenital anomalies, and macrosomia, play a relatively unimportant role in the morbidity and mortality of these infants.

1. Respiratory Distress: Although it has been apparent for some time that many of the infants of diabetic mothers have severe respiratory distress, it has always been difficult to assess these changes quantitatively. The experiences with the present series are tabulated in Table 35.

Approximately one-third of all infants of diabetic mothers develop clinical respiratory distress. The majority of these symptoms become detectable to the careful observer in the first 6 hours of life and generally persist for from 24 to 48 hours of age. The principal signs are hoarseness and coughing, a constant complaining cry, retraction of the anterior chest wall, and, in the severer cases, cyanosis even in the presence of oxygen. These symptoms either progress until the infant dies, at 36-48 hours of age, or regress, in which case the remainder of the neonatal course is uneventful. Long-term follow-up of such infants with respiratory distress has revealed no increased incidence of pulmonary disease or sequelae.

In 1956, Miller [140] and Haddad, Hsia, and Gellis [86] suggested the use of respiratory rates as an objective means of measuring respiratory distress in newborn infants. The latter showed that the mean respiratory rate in infants of diabetic mothers was 20-25 per minute faster than that of a group of normal full-term infants. The differences were highly significant (more than 10 standard errors between the means). In this same study, they showed that respiratory rates of more than 60 per minute are very unusual in normal infants and suggest some physiological or chemical disturbance. Since 1954, we have measured the respiratory rates in 171 infants of diabetic mothers at 2-hour intervals for the first 72 hours of life. The results of this study are shown in Table 36. It was found that 55% of these infants showed rates of respiration exceeding 60 per minute. This suggests that by using this method of measurement it is possible to demonstrate changes in respiration in an even larger group of infants than on the basis of the clinical signs described above.

TABLE 36.—*Respiratory Rates in Infants of Diabetic Mothers*

Respiratory Rates,* No/Min.	No.	%
0-60	77	44.5
60-100	70	40.5
100+	24	14.0
Total	171	

* Average of measurements taken at two hourly intervals for first 48 hours, and at four hourly intervals for next 24 hours.

2. Hypoglycemia: The problem of hypoglycemia in the infant of the diabetic mother has given rise to considerable controversy. In the 1930's, sporadic reports appeared showing that these infants had blood sugar levels soon after birth which

were abnormally low when judged by adult standards.[131,160] Later, Hartmann and Jaudon[91] demonstrated that this occurred in all newborn infants but tended to be severer among diabetic infants. This view has been shared by several other workers,[110,150,183,195] and some have recommended oral or parenteral glucose therapy as a means of prophylaxis.[11,183] Others have found no difference in the blood sugar levels between diabetic and nondiabetic infants.[174,178,209] More recently, Farquhar[70,71] has shown that this hypoglycemia is very transient, lasting only two to three hours after birth. More important, he feels that there is no relationship between the development of an abnormal neonatal course and the blood sugar level at the time or the extent and rapidity of the fall.

In the present series, clinical hypoglycemia accompanied by a blood sugar level of less than 40 mg. % has only been encountered on two occasions. One infant was found to have a cord blood sugar of 12 mg. % and subsequently died. No postmortem examination was performed. The other was found to have a blood sugar of 24.6 mg. % in the first three hours of life and responded satisfactorily to intravenous dextrose therapy. The serial blood sugar determinations performed on about 100 infants of diabetic mothers in our series are summarized in Table 37. It is apparent that hypoglycemia is a rare occurrence in this series, and in general the blood sugar levels are similar to those seen in normal newborn infants. The higher levels in the first three-hour period are undoubtedly due to the withholding of insulin and the administration of dextrose intravenously to the mothers prior to delivery.

TABLE 37.—*Blood Sugar Levels in Infants of Diabetic Mothers*

	Hr. After Birth		
	0-3	3-6	6-12
Determinations, No.	104	100	94
Mean	107.9 mg. %	88.4 mg. %	89.6 mg. %
S. D.	±30.2 mg. %	±36.6 mg. %	±26.9 mg. %
Range	24.6-220 mg. %	17.4-156 mg. %	43.8-189 mg. %

TABLE 38.—*Incidence of Lethal Congenital Anomalies in Infants of Diabetic Mothers*

	Births, No.	Lethal Anomalies, No.
Gellis & Hsia	711	13
Pederson & Brandstrup [117]	205	8
Jones [103]	165	6
Peel & Oakley [182]	142	9
Hurwitz & Higano [91]	140	5
MRC [106]	136	6
Hall & Tillman [89]	104	0
Total	1,663	47 (2.9%)

In a separate investigation, we have analyzed blood samples for fermentable and nonfermentable sugar in both normal infants and infants of diabetic mothers.[56] It was found that no significant difference in proportions exists between the two groups and that there is no evidence of a low true glucose in the infant of the diabetic mother.

3. Congenital Anomalies: The incidence of congenital anomalies varies from one clinic to another, depending upon the method for classification of severity. However, there is universal agreement upon the definition of a lethal congenital anomaly, in that the infant died presumably as a result of a serious malformation. The incidence of lethal congenital anomalies among the various larger series of infants of diabetic mothers is summarized in Table 38. The over-all incidence of 2.9% is considerably higher than that of 0.94% reported by Peel and Oakley, in England,[182] and the 0.75% reported by Reid, at the Boston Lying-in Hospital,[141] among normal infants. However, it should be remembered that even with this increased incidence, congenital malformations account for a very small proportion of the deaths in infants of diabetic mothers.

4. Macrosomia: Miller[136,149,153] has demonstrated cardiac enlargement in infants

of diabetic mothers on the basis of x-ray findings and weight of the organ at postmortem examination. He has suggested that the high incidence of neonatal mortality in this group may be due to some type of heart failure. Similar observations have been made by Warren and LeCompte [241] and by Cardell [39] in some of the infants studied at postmortem examination. The former found that 19 of 41 infants of diabetic mothers had a cardiac weight which was more than 2 standard deviations above the calculated weight. The latter, using a formula devised by Miller, found that in 4 out of 25 infants the heart exceeded the calculated weight by 3 standard deviations. However, in none of these instances was excessive glycogen taken into consideration.

With the possible exception of the heart, there is little evidence of a generalized increase in the size or weight of body organs. Cardell [39] concludes as follows: "The increase of organ weight is only apparent and is related to the increase of body weight. In many of the reports of visceromegaly in these infants, two errors have been made. Firstly, comparison with average figures for the organ weights instead of with the normal range; and secondly, comparison with infants of similar gestational age instead of with infants of similar body weight."

5. Gastric Content: In 1949, Gellis, White, and Pfeffer [78] reported an increase in the gastric content among infants of diabetic mothers delivered by cesarean section. Using the same technique for gastric suction, they obtained an average of 20 ml. from 25 infants of diabetic mothers, as compared with 14 ml. from 12 infants of nondiabetic mothers. A similar increase was noted among those delivered by the pelvic route, with the diabetic infants having about 5 ml. and the nondiabetic infants having 2 ml.

In the same study, Gellis et al.[78] showed that of the 25 infants receiving gastric suction at birth, 4 showed respiratory embarrassment that was present at birth and none developed delayed respiratory difficulty. Of the 25 infants in whom suction was not performed, 15 developed respiratory difficulty; in 6 it was present at birth, but 9 of the 15 showed a delayed onset of obstructive signs. Subsequent studies by Little and his co-workers [122] and by Freeman and Scott [74] among nondiabetic infants continue to show a beneficial effect from gastric suction. The volumes of the gastric content in the present series are given in Table 39.

TABLE 39.—*Volume of Gastric Contents in Infants of Diabetic Mothers*

Gastric Content, Vol.	No.
Less than 10 ml.	210
11-20 ml.	156
More thn 20 ml.	61
Not done	295
Total	722

A large controlled series of infants of diabetic mothers is needed, however, in order to evaluate the possible beneficial effect of this procedure on morbidity and mortality figures.

C. Laboratory Data.—1. Blood Cell Counts: The hematologic findings in approximately 100 infants of diabetic mothers in the present series are tabulated in Table

TABLE 40.—*Blood Cell Counts in Infants of Diabetic Mothers* *

	Hgb., % (95)	RBC, Million/ Cu. Mm. (100)	WBC/Cu. Mm. (94)	Polymorphonuclears, % (98)	Lymphocytes, % (98)	Eosinophils, % (98)	Monocytes, % (98)	Basophils, % (98)	Reticulated RBC/100 WBC (73)
Mean	116.7	5.80	18,100	58.0	34.2	1.6	4.1	0.6	14.7
S. D.	±9.8	±0.55	±6,300	±6.6	±5.0	±2.6	±6.1	±2.3	±3.1
Range	82-150	3.5-7.2	6,400-34,000	29-80	8-58	0-13	0-14	0-18	0-210

* Number of determinations is given in parentheses.

40. The hemoglobin, red cell blood count, white cell blood count, and differential counts do not differ significantly from the values usually seen in normal infants on the first day of life.

Anderson [5] has reported that the number of nucleated red blood cells averages about 7.3 per 100 white cells in full-term infants and 21 per 100 in prematures. The count in these infants would appear to fall somewhere between the two. Miller [149] has suggested that the high percentage of nucleated red cells in the infant of the diabetic mother may be due to a mechanism similar to that in erythroblastosis fetalis. More recently, Berglund and Zetterstrom [23] have suggested that such infants suffer from hypoxia, and this may represent an attempt on the part of the fetus to raise its oxygen-carrying capacity.

2. Roentgenographic Studies: Peterson [184] has undertaken a detailed study of the chest films taken on 84 consecutive infants of diabetic mothers in one series; using the criteria for hyaline-membrane disease previously described by Peterson and Pendleton [184] and others,[55,135,220] he classified each patient as being either normal or abnormal. The correlation between clinical disease and roentgenographic appearance is shown in Table 41. It can be seen that agreement

TABLE 41.—*Correlation Between Clinical Hyaline-Membrane Disease and Roentgenographic Appearance*

	Chest X-Ray		
	Normal	Abnormal	Total
Clinically normal	45	8	56
Clinical evidence of hyaline-membrane disease	10	18	28
Total	58	26	84

was found in about 80% of the cases.

In the same study, definite cardiac enlargement on the basis of PA diameter was noted in 3 out of the 84 patients. Two of these patients subsequently died of congenital heart disease; the third died of hyaline-membrane disease but showed no unusual cardiac findings at postmortem examination.

3. Electrocardiographic Studies: Electrocardiograms were routinely performed on about 50 infants of diabetic mothers. No abnormalities could be found in any of the tracings. Bjorklund [26] has undertaken a similar study on 15 infants of diabetic mothers. In 11 of these, he noted an abnormality characteristic of hypopotassemia. These findings remain to be confirmed.

4. Electrolyte Changes: In 1954, Lowrey, Graham, and Tsao [84,125] reported the finding of uncompensated acidosis in infants (of diabetic mothers) less than 24 hours old. This was characterized by a lowered blood pH and a high pCO_2 in plasma. This phenomenon has since been confirmed by Reardon and her co-workers [194] and by Segal and his co-workers [202] in the present series of patients. The data on the latter study which was performed on our patients are summarized in Table 42.

TABLE 42.—*Mean Values of Blood Electrolytes in Infants of Diabetic Mothers in the Neonatal Period* *

	pH	CO_2 Content, mEq/L.	pCO_2, Mm. Hg	O_2, % Saturation	Lactate
Cord artery	7.09 (21)	25.4 (13)	82 (13)	14 (22)	25 (25)
Cord vein	7.15 (29)	23.2 (17)	68 (17)	37 (35)	20 (27)
1 hr.	7.26 (6)				18 (17)
4 hr.	7.28 (8)				12 (16)

* The number of determinations is given in parentheses. (Reproduced with permission of Dr. Segal) [202]

Reardon et al.[194] have also indicated that at 4 hours of age, in addition to respiratory acidosis, there is also a metabolic acidosis as indicated by a decreased plasma CO_2 content. However, this is not more marked, generally, than that seen in normal infants at the same age.

It has been generally noted that the respiratory distress in the neonatal period has usually been most marked in those infants with moderate to severe uncompensated respiratory acidosis.[194,202] This is in agreement with the observations of Miller

and his co-workers on premature infants.[144] Because of this, Reardon[194] has compared the clinical data on infants of diabetic mothers during two study periods. From 1953 to 1955, eighteen infants were given 10% glucose water either parenterally or by mouth, and they received no saline. Six of these infants died, and all were found to have pulmonary hyaline membranes at postmortem examination. On the other hand, in the period 1951 to 1957, thirty-seven infants were given 31 ml. of 5% glucose per pound and 0.45 gm. % of saline daily. Only 3 of these infants died, one with pulmonary hyaline membranes at 4 hours, one with hypoglycemia and infection at 7 days, and one at 21 days, possibly as a result of sepsis. The difference in the death rate associated with pulmonary hyaline membranes in the two groups is significant at the 1% level.

Other electrolytes, including sodium, potassium, chlorides, and total base have been measured by Lowrey and his co-workers,[125] by Clayton,[43] by Zetterstrom and Aberg,[262] and in our laboratory. All have been found to be within normal limits. In balance studies, Zetterstrom and Aberg have noted a continuous loss of sodium, potassium, and chloride through the urine during the first few days of life. However, if electrolytes are administered, there is a retention of potassium but a continued loss of sodium. This would appear to correlate with the clinical disappearance of edema during the newborn period.

5. Oxygen Saturation: Careful observations on oxygen saturation in the umbilical cord of infants of diabetic mothers have been made by Berglund and Zetterstrom[23] and by Segal and his co-workers.[202] Both groups found that the oxygen content in the umbilical vein is lower than in control pregnancies. The data from the present series are given in Table 42.

6. Adrenal Function: Both Bjorklund[27] and Farquhar[72] have studied the adrenal function of infants of diabetic mothers. They have found that there is an increase of corticoids in the urine. The former also found a normal Thorn test (response of eosinophils to corticotropin [ACTH]), and the latter showed that the total eosinophil count fell more rapidly in the first six hours than among normal infants. All this suggests that adrenal function in such infants is not only adequate but may be increased, and this in turn produces the distinct morphological features in the fetus from the diabetic mother.

D. Pathological Features.—The postmortem examination findings in the infant of the diabetic mother have been described in detail by Warren and LeCompte[241] and Cardell.[39] The principal changes include (1) the presence of pulmonary hyaline membranes,[39,123,241,258] which are similar to those seen in premature infants and those delivered by cesarean section[19,30,80,115] and those produced experimentally in animals[19,21,81,97]; (2) excessive deposits of glycogen in various body organs,[39,241] and (3) hypertrophy of the islets of Langerhans in the pancreas.[40,85,92,130,149,153,163,165,189]

The data on 104 infants (of diabetic mothers) in the present series who died are summarized in Table 43. Of these, 31 were known to have succumbed from specific causes. These included 13 who had lethal congenital anomalies, 9 who had severe intracranial hemorrhages, 4 with sepsis, and 5 with miscellaneous causes for death. Of the remaining 73 infants, pulmonary hyaline membranes with or without atelectasis were the only anatomical findings. The detailed pathological description of these infants will be presented in a companion paper.[57]

E. Summary.—From the above survey, it would appear that hypoglycemia, infections, and congenital anomalies do not play a significant role in the high neonatal mortality among infants of diabetic mothers. Instead, most of the deaths, especially in the more premature infants, are associated with the presence of pulmonary hyaline membranes at postmortem examination. Other factors which may play a role in their pathogenesis are (1) excessive size and

TABLE 43.—*Summary of 104 Infants of Diabetic Mothers Who Died*

Case	Sex	Birth Weight, Lb. Oz.	Gestation, Wk.	Diabetic Class	Mode of Delivery	Age at Death, Hr.	Contributing Factors	Postmortem Findings
				I(*a*). Deaths Associated with Major Congenital Anomalies				
1	F	8-1	34	C	CS	2 wk.	--	Thrombosis aorta, encephalocele, hydroceph.
2	M	5-10	37	D	CS	3½ wk.		Complete transposition of great vessels
3	F	--	36	D	CS	15	--	Intraventricular septal defect
4	M	7-2	37	B	P	2½ wk.	--	Intraventricular septal defect
5	F	6	36	C	CS	14	--	Cor biloculare, multiple congenital anomalies
6	F	6-12	37	D	CS	72	Premature separation of placenta	Coarctation of aorta * (distal to ductus)
7	M	4-6	37	C	CS	½	--	Sireniform monster
8	M	8-10	35	C	P(S)	12 wk.	--	Intraventricular septal defect
9	M	5-9	36	C	CS	40	--	Multiple congenital defects
10	M	6-11	35	D	CS	96	--	Tracheoesophageal fistula
11	M	6-12	35	D	CS	11	--	Malrotation of heart
12	F	5-11	35	E	CS	2 wk.	--	Intra-auricular septal defect
13	M	4-4	36	C	P(S)	4 wk.	--	Hypoplasia of kidneys
				I(*b*). Deaths Associated with Intracranial Hemorrhage				
1	F	6-8	40	B	P	6	Breech extraction	Tentorial tear
2	F	6-14	34	C	CS	24	--	Tentorial tear
3	F	4-3	34	D	CS	24	--	Subdural hemorrhage
4	M	3-1	32	D	P(S)	24	Twins	Falx tear
5	F	1-4	29	C	P(S)	12	--	Subdural hemorrhage
6	F	4-10	34	C	CS(S)	72	--	Subependymal hemorrhage. (subendocardial fibroelastosis)
7	M	3-15	35	B	P(S)	72	--	Intraventricular hemorrhage
8	M	3-15	31	B	P(S)	25	--	Intraventricular hemorrhage
9	F	3-3	32	D	P(S)	36	Twins	Subarachnoid hemorrhage
				I(*c*). Deaths Associated with Infections				
1	M	7-4	38	C	CS	24	--	Pneumonia
2	M	7-3	36	D	CS	48	--	Pneumonia
3	F	3-6	35	F	P(S)	36	--	Sepsis, pneumonia, Escherchia coli
4	F	2-10	32	D	P(S)	120	Twins	Pulmonary hemorrhage
				I(*d*). Deaths Due to Other Specific Causes				
1	M	6-3	34	C	CS	44	--	EF with KI
2	F	4-8	36	D	CS	4	--	Pneumothorax following jugular puncture
3	M	6-12	35	C	CS	20	Cord blood sugar 12 mg. %	--
4	M	6-14	36	C	P(S)	19	--	Adrenal hemorrhage
5	F	5-5	35	D	CS	30	--	Aspiration asphyxia
				II(*a*). Deaths Without Known Cause in Previable Infants				
1	M	4	28	C	P(S)	½	--	At
2	M	3-13	24	C	P(S)	24	--	At/HMD
3		2	24	B	P(S)	8	--	At/HMD
4	M	1-7	26	F	CS	20	Done for interruption of pregnancy	--
5	F	2-2	26	B	P(S)	7	Twins	--
6	F	1-15	26	B	P(S)	3	Twins	--
7	M	2-2	26	D	P(S)	2	--	At
8	M	1-14	28	E	P(S)	30	Twins	--
9	M	1-8	28	E	P(S)	30	Twins	--
10	M	3	28	C	P(S)	24	--	At/HMD
11	F	1-12	27	C	P(S)	16	Twins	At/HMD
				II(*b*). Deaths Without Known Cause Where Prematurity May Be a Factor				
1	M	3-11	31	C	CS	33	--	At/HMD
2	F	3	31	C	P(S)	8	--	--
3	F	3-4	32	D	P(S)	1 wk.	Twins	At/HMD
4	M	4-1	31	D	CS	24	--	At/HMD
5	M	3-3	32	B	CS	7	Placenta previa	At/HMD
6	M	3-10	30	D	P(S)	8	--	At/HMD
7	M	3-3	30	D	CS	72	Done for interruption of pregnancy	At/HMD

TABLE 43.—*Summary of 104 Infants of Diabetic Mothers Who Died* (Continued)

Case	Sex	Birth Weight, Lb. Oz.	Gestation, Wk.	Diabetic Class	Mode of Delivery	Age at Death, Hr.	Contributing Factors	Postmortem Findings
8	M	3-4	30	D	P(S)	48	--	At/HMD †
9	M	4-2	32	B	P(S)	10	Premature separation of placenta	At/HMD
10	F	3-1	31	B	P(S)	12	--	At *
11	F	4-1	33	B	CS	12	--	At/HMD
12	M	4	32	C	P(S)	13	--	At/HMD
13	F	4-13	33	D	CS	30	Loss of fetal activity	At/HMD
14	M	3-11	33	D	P(S)	10	--	At/HMD
15	F	4-7	31	D	P(S)	31	--	At/HMD
16	F	4-8	33	D	P(S)	24	--	At/HMD
17	M	3	29	C	P(S)	14	--	At/HMD
18	M	4-3	33	C	CS	7	Premature separation of placenta	--
19	F	4-5	32	C	P(S)	24	--	At/HMD
					II(c). Deaths Without Known Cause in Mature Infants			
1	M	5-1	32	B	P(S)	8	--	At/HMD
2	M	5-13	32	D	P(S)	24	--	At/HMD *
3	M	7-12	36	D	CS	24	--	At/HMD
4	M	7-3	35	B	P(S)	72	--	--
5	M	5-14	35	D	CS	41	--	At/HMD *
6	M	6-8	36	C	CS	24	--	At/HMD †
7	F	5-13	35	B	CS	24	--	At/HMD
8	F	6-6	31	C	CS	12	--	At/HMD
9	M	5-4	34	C	CS	13	--	At *
10	F	7-4	37	D	CS	24	--	At/HMD *
11	M	5-4	36	B	CS	96	--	At/HMD
12	M	5-7	36	B	CS	48	--	At/HMD
13	F	6-1	37	C	CS	70	--	At/HMD *
14	F	8-10	37	C	CS	96	--	At/HMD
15	M	5-7	38	B	P	24	--	At/HMD
16	M	6-7	37	D	CS	37	--	--
17	M	8-4	35	B	CS	24	--	At/HMD
18	M	6-13	37	C	CS	36	--	At/HMD
19	F	6-13	34	B	P(S)	33	Diabetic coma in mother in 34th wk.	At/HMD
20	F	6-8	35	D	CS	18	--	At/HMD
21	F	6-15	34	D	CS	42	--	At/HMD
22	F	5-9	35	B	P(S)	48	--	At/HMD
23	M	6-10	34	F	CS	19	--	At/HMD
24	M	7-12	37	D	P	20	--	At/HMD *
25	M	6-6	35	D	CS	9	No fetal movement	At/HMD
26	M	4-4	36	F	CS	21	--	At/HMD
27	M	5-3	36	B	CS	41	--	At with aspirate *
28	M	6-12	35	D	CS	53	--	At/HMD *
29	M	4-12	35	D	CS	48	--	At/HMD *
30	M	9-12	36	C	CS	4	--	At
31	M	5	33	F	CS	96	--	At/HMD
32	M	5-12	36	D	CS	32	--	At/HMD
33	M	7-10	35	C	CS	25	--	At/HMD *
34	M	6-10	33	C	P(S)	20	--	At/HMD
35	F	5-10	35	F	CS	1	--	At
36	M	6-10	35	D	P	10	--	At/HMD
37	F	5-10	34	F	CS	½	Loss of fetal movement	At
38	M	3-12	35	F	CS	18	--	At/HMD
39	F	8-9	37	C	CS	45	--	At/HMD
40	F	4-4	33	F	CS	21	--	At/HMD
41	F	5-2	36	D	CS	9	--	At/HMD
42	M	8-3	37	D	CS	20	--	
43	F	6-10	37	D	CS	24	--	

* Some bronchopneumonia also present but not sufficient to account for death.
† Small intracranial hemorrhage present but not sufficient to account for death.
‡ CS=Cesarean section; P=Pelvic; P(S)=Spontaneous pelvic.
§ At=Atelectasis, HMD=Hyaline Membrane Disease

weight (for the period of gestation), (2) increased gastric content at the time of birth, and (3) biochemical changes suggestive of acidosis. Boys also appear to be more susceptible to this complication than girls.

VII. Pulmonary Hyaline-Membrane Disease

Before proceeding to a detailed discussion on the clinical management of the infant of the diabetic mother, it is essential that we consider some of the current concepts on the pathogenesis of pulmonary hyaline-membrane disease in young infants.

De and Anderson [51] have reviewed all of the pertinent literature on this subject up to 1953. Since then, there have been additional pathological descriptions of the entity [33,80,87,237] and attempts to correlate these pathological findings with clinical changes.[6,21,41,90,114,115,197,199,204,258] There is general agreement that the syndrome appears primarily among premature infants, infants suffering from distress in utero, infants delivered by cesarean section, and infants of diabetic mothers.

Investigative work on the etiology of hyaline-membrane disease may be divided into two main types: (1) studies on the nature of the membrane and its pathogenesis and (2) chemical and physiological changes associated with hyaline-membrane disease.

A. Membrane Formation.—Nature of Hyaline Membrane and Its Pathogenesis: For many years, it was believed that the aspiration of amniotic fluid in utero and at delivery was responsible for hyaline-membrane formation.[67] However, several attempts at injecting amniotic fluid into the trachea failed to produce the characteristic histologic picture in the lungs.[4,53,68,146] In 1951, Blystad, Landing, and Smith[30] showed that if 15 to 20 ml. of amniotic fluid was injected in 1 ml. amounts into excised guinea pig and mouse lungs, which were alternately expanded and contracted for one hour by air pressure of 1 lb., a thin hyaline membrane was produced in some alveoli. These observations have been confirmed by essentially similar experiments conducted by Claireaux,[41] Hadders and Dirken,[87] and Laufe and Stevenson.[116]

Hyaline membranes can also be experimentally produced by oxygen poisoning.[9,42,186] In 1951, Bruns and Shields[36] placed three adult and nine infant guinea pigs in 98% oxygen under normal atmospheric pressure conditions. All three adult guinea pigs developed hyaline membranes. Three of the five newborn guinea pigs also developed hyaline membranes; however, none of the four intrauterine fetuses in one adult guinea pig's uterus during the experiment showed hyaline-membrane formation. These experiments have more recently been repeated by the same authors,[37] De and Anderson,[52] and Lynch et al.[129] with essentially the same results. Ingalls [100] has suggested that an imbalance in the supply of oxygen may be responsible for hyaline-membrane disease, much as it is for retrolental fibroplasia in premature infants.

Hyaline-membrane disease has also been produced by bilateral vagotomy,[66,143] x-ray irradiation,[240] and carbon dioxide poisoning.[17]

The chemical nature of the membranes has been a matter of considerable speculation. Lynch and Mellor [126,127,128] have shown that the membranes contained a hemoglobin-like compound which stained by the Lepehne-Pickworth and Nadi reactions. They suggested that the heme in the membranes must come either from lysed extravasated red blood cells or from the mucosal epithelial cells of the respiratory bronchioles and alveolar ducts. Duran-Jorda and his coworkers [60] have undertaken similar studies using mercury-vapor light spectra and concluded that the hyaline material results from an exudative process through the capillary walls.

In 1956, Gitlin and Craig [81] studied the lungs from five newborn infants who died because of respiratory difficulties associated with hyaline membranes. By means of fluorescent-antibody and dye-staining procedures, they were able to demonstrate that

the membranes in these infants were composed largely of fibrin.

For some years, it had been believed that respiratory distress and hyaline-membrane formation may be associated with cardiac failure. In the 1940's, Miller [120,141,153] suggested that cardiac failure was in part responsible for the death of infants of diabetic mothers. More recently, Lendrum [120] has suggested that the pulmonary hyaline-membrane syndrome is a manifestation of heart failure in the newborn infant. He points out that when the placental circulation is cut off and the newborn infant takes his first breath, several important changes occur. Before birth, about half of the blood pumped into the aorta passes through the placenta. When the return of this blood through the umbilical vein ceases, the volume that the right atrium must pump is reduced and this causes a fall in the pressure that had previously kept open the valve flap of the foramen ovale. The pressure in the right ventricle also falls when inflation of the lungs makes the pulmonary circuit an outlet with relatively low resistance. In the left heart, the rush of blood into the left atrium from the pulmonary veins increases the pressure in this chamber and ensures a physiological closure of the valve of the foramen ovale. The pressure in the left ventricle is increased when the circulation from the placenta is cut off. Since the pulmonary vascular bed, the left ventricle, and the circular muscle of the ductus arteriosus are incompletely developed, there may be a congestion of the pulmonary vessels. This in turn will result in a rise in pulmonary blood pressure as soon as there is any sizable increase in pulmonary blood volume.

Both Laufe and Stevenson [116,230] and Gitlin and Craig [81] have proposed that hyaline membranes form because (1) there is an effusion from the pulmonary circulation (This could occur possibly because of the mechanism postulated by Lendrum above; also, Sutherland and his co-workers [231] have observed an increased permeability of other tissues in premature infants and those with respiratory distress.), (2) once the effusion has crossed the membranes, the fibrinogen in the plasma reacts with the thromboplastin in the aspirated amniotic fluid to form fibrin, and (3) finally, there is a syneresis of the fibrin to form a membrane.

B. Chemical and Physiological Changes.

In the previous section we have described the chemical changes which are seen in the infant of the diabetic mother.[125,193,194,202] Miller et al.[144] and Blystad [28-30] have noted similar changes in nondiabetic infants.

In experimental animals, Lynch and his co-workers [126] have noted a fall in blood pH, a rise in serum potassium and inorganic phosphate, and, in four instances, a moderate rise in blood creatinine. Bain, cited by Lynch,[129] has suggested that these changes might occur because of some form of intrapulmonary respiratory obstruction. This would also go with the concept proposed by Reardon et al.[194] that in infants with respiratory distress there exists first a respiratory acidosis at birth and subsequently a metabolic acidosis at about 4 hours of age.

Most of the physiological changes can be attributed to disturbances in gas diffusion across the respiratory epithelium. This can be caused by two factors. First, there is the lack of exchange due to the hyaline membranes themselves. Second, there is an additional obstructive factor. Craig, Fenton, and Gitlin [47] have recently shown that in lungs with hyaline membranes no expansion of the terminal alveoli occurs, even though the alveolar ducts are greatly overdistended.

The physiological changes associated with hyaline-membrane disease have been worked out by Cook and his co-workers.[44-46,107] They state:

> The change necessitates an increase in minute volume to maintain alveolar ventilation. This adjustment is accomplished primarily by an increase in respiratory rate; presumably, the marked reduction in compliance (1 or 2 ml. per cm. of water pressure as compared to 5 ml. for the normal infant) makes it impossible for the infants to increase their tidal volume significantly....
>
> As a result of increased rate and decreased lung compliance the necessary ventilatory adjustments

are only made at the expense of very great respiratory efforts and pulmonary work of respiration is increased to 200 to 400 per cent above the normal level. Although this increased work may be relatively insignificant compared to the entire body metabolism, it may lead to exhaustion of the respiratory muscles themselves and to further anoxia, hypercapnia, and death.

Observations on the clinical course and outcome of infants with hyaline-membrane disease are in total agreement with these physiological findings.

In summary, the etiology for hyaline-membrane formation in newborn infants is still unknown at the present time. It would appear that the aspiration of amniotic fluid, changes in cardiovascular dynamics immediately after birth, and increased permeability of body tissues may each play a role in their formation. Chemically, this results first in a respiratory acidosis and subsequently in a metabolic acidosis. Physiologically, the increase in minute volume eventually causes an increase in exhaustion. The possible role of oxygen concentration in formation of membranes pulmonary work and eventually death from remains to be determined.

VIII. Clinical Management

Despite the voluminous literature that has been written concerning the infant of the diabetic mother, there is very little evidence that any one therapeutic approach decisively affects the prognosis and outcome of such pregnancies. In the following section, we shall outline our clinical experiences in the management of several hundred such infants.

A. General Measures.—We wish to emphasize first in the strongest possible terms that the management of a diabetic pregnancy should be a team effort. We are convinced by both personal experience and statistical analysis that the only significant factor that has been responsible for any reduction in fetal mortality during the past 20 years is the acceptance of a team approach. Ideally, a team should consist of an internist, two obstetricians, an anesthetist, and a pediatrician who follow the case throughout the pregnancy and after delivery. Furthermore, the best results are obtained by a team which has worked together many times, since experience seems to make a difference.

Since this review is being done primarily from the pediatric viewpoint, we shall not dwell at any length on prenatal management. In general, most investigators agree upon (1) good diabetic control; (2) careful follow-up of the mother throughout pregnancy and admission to the hospital for a period prior to delivery; (3) delivery between the 35th and 36th weeks of gestation, if possible, and (4) if the cervix appears to be favorable, attempted trial of labor for a short time before resorting to cesarean section. We do not wish to enter into the controversy over female sex hormones except to state that evidence that they produce a significant reduction in the incidence of stillbirths or neonatal deaths remains to be presented.

On the day of delivery, insulin should be withheld. An intravenous drip of 10% dextrose should be started prior to delivery. In our clinic, spinal or caudal anesthesia is used when possible. At the time of delivery, all members of the team are present and their role is clearly assigned.

The pediatrician takes the infant from the obstetrician as soon as the cord is clamped and places the infant in a bassinette with the head at a lower level than the feet. The infant is immediately wrapped in a previously warmed blanket. By means of a catheter attached to a Kreselman resuscitator, the nasopharynx is gently aspirated and the airway cleared. If the infant does not breathe spontaneously, resuscitation by gentle massage of the back and flicking of the toes is undertaken. Oxygen by mask is also administered should the infant appear cyanotic. More vigorous resuscitative measures, such as slapping of the back, the administration of oxygen under positive pressure, or mouth-to-mouth insufflation, have seldom been necessary. Likewise, we rarely have to use epinephrine or caffein and sodium benzoate to resuscitate an infant.

As soon as a satisfactory airway is established, the gastric contents are removed and the infant is quickly placed in a preheated incubator and transferred to the premature nursery. We then usually leave the infant strictly alone for the first 48 hours of life. It is our clinical impression that infants of diabetic mothers as well as normal infants should not be subjected to repeated examinations and manipulations during this critical period and that the less one does for the infant, the better the outcome.

If the infant progresses well and has no respiratory distress, feedings are started on the third day. In the smaller infants, this is done by gavage; in the larger infants, bottle feedings are used. Most infants tend to go through a two- to three-week period of lethargy and poor feeding with accompanying poor weight gain. After that, they behave much like normal infants and cannot usually be distinguished from them. As a rule, the infants of diabetic mothers are discharged from the hospital when the weight reaches 5½ lb. or more.

B. Specific Measures.—This remains the area of greatest controversy, and it is hoped that our personal experiences with a rather large series of infants will help to resolve some of it.

1. Gastric Suction: In 1949, Gellis, White, and Pfeffer [78] proposed the use of gastric suction immediately after birth as a means of preventing respiratory distress. This approach has been endorsed by Little and his co-workers [122] and by Freeman and Scott.[74] On theoretical grounds, there is something to be said for its use. Emptying the stomach of swallowed amniotic fluid certainly prevents further aspiration of the material and presumably would reduce the conversion of fibrinogen to fibrin in the alveoli. Furthermore, it appears to be a relatively benign procedure and reduces the great tendency of these infants to regurgitate amniotic fluid and mucus during the first 24 hours, and, finally, it serves to diagnose promptly the rare case of esophageal atresia.

2. Withholding Feedings: Although several workers have reported transient hypoglycemia in infants of diabetic mothers [110, 150,183,195] and have recommended the prophylactic administration of oral glucose or parenteral dextrose,[11,195] true hypoglycemia appears to be an extremely rare occurrence. We have felt that the danger of aspiration in infants with respiratory distress outweighs whatever value early feedings might have in preventing hypoglycemia.

The work of Reardon and her associates [194] suggests that the respiratory distress in infants of diabetic and "prediabetic" mothers occurs in association first with a respiratory acidosis and subsequently with a metabolic acidosis. Their report that infants treated with 30 ml. per pound per day of 5% dextrose and 0.45% saline by mouth or parenterally showed marked clinical improvement and a return of arterial pCO_2 to normal within 24 hours is of great interest. If confirmed by other workers, the recommendations should be generally adopted.

3. Chemotherapy: In our clinic, we have routinely placed each infant on prophylactic antibiotic therapy. We have found that aqueous penicillin, 100,000 units, and streptomycin, 50 mg., mixed in the same syringe and given intramuscularly twice daily is the least traumatic method of administration. It is felt that this may be of value in reducing secondary bacterial infections. Unfortunately, we have seen no significant reduction in the incidence of respiratory distress and death from hyaline-membrane disease in recent years as compared with the preantibiotic era. In view of the increase in resistant organisms in most nurseries, there is little argument in favor of prophylactic antibiotics and it is our present feeling that antibiotics should be administered therapeutically only.

4. Oxygen: Although Bruns and Shields [36,37] and De and Anderson [52] have shown that high concentrations of oxygen are responsible for hyaline-membrane formation in experimental animals, this relationship remains to be demonstrated in

newborn infants. In our own series, we maintained the oxygen flow to the incubator at 8 liters per minute during the period 1950-1953 and reduced the flow to 4 liters per minute during the period 1954-1956. During the period when the infants were exposed to a higher oxygen concentration, there were 29 neonatal deaths in 204 live-born infants. In the latter period, there were 25 neonatal deaths in 169 live-born infants. The differences are not statistically significant χ^2 [1 *d. f.*] = 0.2).

At the present time, we believe that unless the infant is cyanotic or suffering from significant amounts of respiratory distress, he should receive no oxygen. If distress with cyanosis develops, oxygen will be needed, and the concentration within the incubator should not exceed 40% saturation. However, should no relief be afforded at this concentration, the flow of oxygen should be increased until the color improves. This will reduce the amount of respiratory work an infant has to perform and may prove to be lifesaving. Although oxygen may be related to hyaline-membrane formation, there is no proof of this relationship in infants at present. Its use cannot be avoided once distress occurs.

5. Mist and Detergents: During the past decade, there has been considerable interest in the use of mist and detergents in the prevention of hyaline-membrane formation. In 1950, one of us (S. S. G.) recommended that infants of diabetic mothers should be placed in an atmosphere of heavy mist produced by passing oxygen through a nebulizer containing water. A few years later, Ravenel [192] advocated the use of Alevaire (detergent solution containing Triton WR-1339 [alkylaryl polyether alcohol], glycerine, and sodium bicarbonate).

The validity of mist and detergents in the prevention of hyaline-membrane disease in newborn infants has been tested by means of a series of controlled clinical trials. In 1955, Silverman and Andersen [206] showed that there was no significant difference in mortality rate among 200 premature infants, half of whom were placed in an atmosphere containing Alevaire and the other half in 90%-100% relative humidity. In 1957, Hsia, Peterson, and Gellis [96] showed no difference in mortality or incidence of respiratory distress in 100 newborn infants of diabetic mothers, half of whom were placed in water-vapor mist (over 100% humidity), as compared with those placed in 50%-70% humidity. Finally, Silverman and Blanc [207] have made a similar study comparing premature infants placed in 80%-90% and 30%-60% relative humidity. Although there was a significantly lower death rate in the former group, the incidence of hyaline-membrane disease found at postmortem examination in both groups was identical. The difference could be due to other factors, such as temperature, and the authors were planning to study further the role of mist in reduction of mortality rate. In view of the potential drying effect of high oxygen concentration and the findings of Silverman's group, we continue to recommend the use of mist for any infant requiring oxygen therapy. If oxygen is not used we see no indication for mist.

6. Other Modes of Therapy: At various times, workers have suggested other methods for the clinical management of the infant of the diabetic mother. Clayton [43] has suggested the use of corticotropin or cortisone. In our own hands, the results have not been successful.[80] In a small controlled study, we noted 1 death in 13 infants treated with cortisone as compared with 3 deaths in 19 controls, a difference which is not significant. Similarly, in comparing the degree of clinical respiratory distress and respiratory rates between the two groups no significant differences could be found.

Others have suggested the use of digitalis or digoxin as a means of treating the hypothetical cardiac failure in infants of diabetic mothers. Although we have used these preparations from time to time, the results have not been impressive. In retrospect, digitalization of these infants may have been too slow to have a beneficial effect. Finally, Townsend [236] has advocated stiffen-

ing the thoracic cage with adhesive tape and splints to prevent retraction and thus oppose intrapleural negative pressure. We have used this approach in one or two instances without success but are in no position to evaluate its use critically.

C. Summary.—At the present time, there is no clear evidence that any specific therapeutic measures are helpful in either the prevention or the treatment of hyaline-membrane disease in newborn infants. Instead, one has to rely on good pediatric care and general supportive measures. It is also apparent that no rational mode of treatment is likely to emerge until we better understand the maternal and fetal factors which are responsible for the pathogenesis of this syndrome.

IX. Summary

We review the available literature and our personal experiences with 934 diabetic pregnancies. The following conclusions may be drawn at the present time:

Pregnancy failures are severalfold more common in women with diabetes mellitus than in normal women. This excessive loss is limited almost exclusively to the period after the 28th week of gestation. Comparison of mortality figures shows little to suggest a significant decrease in the fetal mortality in recent years, and no one group advocating a specific method of management has been able to achieve results which are significantly superior to other clinics. Experience and teamwork seem to be the only factors which influence the ultimate outcome of such pregnancies.

Only two maternal factors appear to influence the fetal mortality: (*a*) the severity of maternal disease and (*b*) good diabetic control. While there is considerable evidence that diabetic women suffer from a hormonal imbalance during pregnancy and that this is frequently associated with the death of the fetus, there is at present no proof that female sex hormones either completely correct this defect or significantly reduce the fetal mortality rate.

Ideally, infants of diabetic mothers should be delivered between the 35th and 36th week of gestation. This prevents the high mortality rate associated with prematurity if delivery takes place too early and the marked increase of stillbirth if delivery takes place closer to term. There is no evidence that the mode of delivery or type of anesthesia used significantly affects the outcome.

Clinically, respiratory distress is the principal complication. A respiratory acidosis followed by a metabolic acidosis appears to occur in association with these respiratory changes. At postmortem examination, pulmonary hyaline membranes and atelectasis are the only findings in two-thirds of the infants who die. Hypoglycemia, infections, and congenital anomalies play a relatively minor role in the high neonatal mortality rate.

No specific therapeutic measures, such as the use of antibiotics, oxygen, mist, or cortisone, are helpful in either the prevention or treatment of hyaline-membrane disease in these infants. Instead, one has to rely on good pediatric care and general supportive measures.

From this study, one must conclude that no rational mode of treatment for the infant of the diabetic mother is likely to emerge until we better understand the maternal and fetal factors which are responsible for the pathogenesis of pulmonary hyaline membranes.

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The Persistent Ostium Primum Atrial Septal Defect

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Recent advances in the treatment of congenital heart disease have been made possible by the concomitant development of more accurate diagnostic techniques. Without this progress in clinical cardiology the ability and skill of the cardiac surgeon would frequently become wasted on useless exploratory operations.

The purpose of this article is to illustrate how an anatomical variation of a relatively common and easily reparable congenital heart lesion [1,2] may be suspected preoperatively and treatment planned accordingly.

In 1956 Blount and his associates published their experience with the ostium primum atrial septal defect and pointed out how this lesion might be recognized clinically.[3] Since that time I have seen two cases of ostium primum type of defect confirmed at surgery which were suspected prior to operation on the basis of criteria outlined by Blount.[3] A third case of ostium primum defect of a slightly different variety, more properly referred to as a partial form of persistent common atrioventricular canal, was seen prior to this article and reviewed subsequently.

Embryology

The ostium primum type of lesion is generally considered to be an atrial septal defect occurring low in the atrial septum, often with maldevelopment of the mitral and tricuspid valves. Embryologically it develops differently from the commoner secundum defect and is due primarily to a lack of development and fusion of the septum primum with the atrioventricular cushions. This results not only in a septal defect but frequently in abnormalities of the atrioventricular valves.[4] It is readily understandable that there is a wide variation possible, extending from the severe common atrioventricular canal to less severe defects of the atrial septum alone with minor variations of the atrioventricular valves. Edwards has emphasized that many of these defects belong in the broad category of partial forms of persistent common atrioventricular canal.[5]

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Report of Cases

The following cases illustrate the clinical and surgical findings seen in the ostium primum type of defect.

CASE 1.—A 27-month-old girl had a cardiac murmur discovered approximately two weeks prior to admission to the Albany Hospital. The patient was delivered prematurely and weighed 4 lb. 8 oz. at birth. The child grew slowly during the first year and weighed 16 lb. at 12 months of age. During the second year of life and especially at the beginning of the third year she showed a definite decrease in exercise tolerance and would frequently climb into bed and rest of her own volition.

In addition, she was bothered by frequent upper respiratory infections and what was described by the mother as bronchitis.

Physical examination revealed a frail blonde child obviously underweight. Examination of the heart revealed the point of maximum impulse in the left sixth interspace in the anterior axillary line. There was a palpable systolic thrill in the fourth interspace along the left sternal border. On auscultation there was a loud harsh systolic murmur heard all over the precordium, loudest in the second and third left interspaces but clearly radiating into the axilla. A medium-pitched Grade 2 diastolic murmur was well heard at the third left interspace and at the apex. The liver edge was palpated 3 fingerbreadths below the costal margin.

Radiography and fluoroscopy showed an increase in the transverse diameter of the heart with con-

siderable increase in the pulmonary vasculature. No intrinsic pulsations were detected. Electrocardiogram was interpreted as showing incomplete right bundle branch block, with some degree of right ventricular hypertrophy. There was a tendency toward left axis and horizontal electrical position.

Cardiac catherization revealed evidence of a large left-to-right shunt at the atrial level. Pulmonary artery pressure was 30/16 mm. Hg, and right ventricular pressure was 38/3 mm. Hg. The femoral artery oxygen saturation was 88%. The lowered oxygen content of the femoral artery blood sample may be due to a technical error or to an increased depth of anesthesia at the time the sample was taken. The femoral artery and cardiac blood samples were not drawn at the same time. There was never any clinical evidence of cyanosis. The catheter was not passed across the defect. Surgical exploration was carried out, and a large ostium primum defect was found, with a regurgitant stream at the mitral valve. With some difficulty the defect was closed, and the patient was returned to her room in fair condition. At 9 p. m. on the evening of surgery the child went into ventricular fibrillation. Resuscitation was unsuccessful, and the patient died. No autopsy was obtained.

CASE 2.—A 10-year-old girl had a heart murmur discovered at the age of 4 years during a routine physical examination. The child had developed normally during the first few years of life, but in recent years there had been a gradual and progressive development of fatigue on exertion, dyspnea, and episodes of chest pain. The child had been troubled by frequent throat and ear infections. Since starting school the patient had been markedly restricted in her activities, and it was difficult to assess her exercise tolerance.

Physical examination revealed no precordial bulge. There were no shocks or thrills palpable. On auscultation there was a Grade 3 medium-pitched systolic murmur heard best in the second left interspace. P_2 was accentuated and widely reduplicated. At the apex a Grade 2 high-pitched blowing systolic murmur was heard that radiated well out into the axilla. This murmur was distinct from the pulmonic murmur. The remainder of the physical examination was unremarkable.

Fluoroscopy revealed enlargement of the right ventricle with questionable enlargement of the left ventricle. The pulmonary vasculature was prominent, and the main pulmonary artery pulsated vigorously. Electrocardiogram showed right bundle branch block with probable right ventricular hypertrophy. There was a tendency toward left axis and horizontal electrical axis.

Catheterization revealed evidence of a left-to-right shunt at the atrial level. The right ventricular pressure was recorded as 48/4 mm. Hg. A pulmonary artery pressure was not obtained because of the development of tachycardia. The catheter was not passed across the defect. The brachial artery oxygen saturation was 91%.

At operation a large ostium primum defect was found, with a definite regurgitant stream at a mitral valve. During the operation supraventricular tachycardia developed which responded to intravenous lanatoside C (Cedilanid), but this recurred postoperatively and persisted for several days despite digitalis therapy. Because of the nature of the defect and the arrhythmia no definitive surgery was attempted on this patient.

CASE 3.—A girl was first seen at the Albany Hospital at the age of 12 years. The mother related a long history of disability beginning at the age of 3 months, at which time the patient developed measles and pneumonia. This illness was followed by five other attacks of pneumonia between the ages of 1 and 12 years. There were numerous episodes of bronchitis in the intervals, often accompanied by epistaxis. At the age of 5 years a diagnosis of rheumatic heart disease was entertained. For two to three years prior to being seen at the Albany Hospital the patient had noticed a marked decrease in exercise tolerance.

Physical examination revealed a thin underdeveloped girl. Examination of the heart disclosed the point of maximum impulse in the left anterior axillary line. There was a systolic thrill palpable at the apex. On auscultation there was a Grade 4 harsh systolic murmur heard all over the precordium. P_2 was markedly accentuated. A diastolic apical murmur was heard intermittently. The remainder of the physical examination was unremarkable.

Radiography and fluoroscopy showed an increase in the transverse diameter of the heart with right ventricular hypertrophy and left atrial enlargement. The main pulmonary artery showed prominent pulsations.

Electrocardiogram showed an incomplete right bundle branch block pattern with right ventricular hypertrophy. There was a right axis and a vertical electrical axis. Cardiac catheterization revealed a shunt at the atrial level. The main pulmonary artery pressure was 53/40 mm. Hg, and the right ventricular pressure was 64/16 mm. Hg. The right atrial pressure curve was not unusual. The catheter was not passed across the defect. The femoral artery sample was 95% saturated. Exploration was carried out, and a low-lying large atrial defect with a forceful systolic jet was found. No attempt at closure was made. Postoperatively the child's temperature ranged between 104 and 107 F, and on the third postoperative day the patient went into congestive heart failure and died. Postmortem examination of the heart revealed a right atrial-left ventricular communication

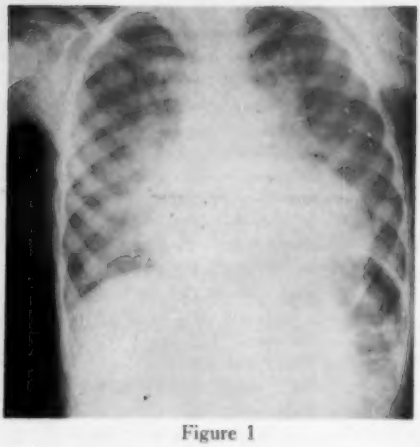


Figure 1

Fig. 1 (Case 1).—Patient with ostium primum defect with mitral insufficiency, showing marked cardiac enlargement.

Fig. 2 (Case 2).—Patient with ostium primum defect with mitral insufficiency, showing marked cardiac enlargement.

Figure 2

with malformation of the anterior two-thirds of the septal leaflet of the tricuspid valve. There was no evidence of aneurysm of the interventricular septum. The mitral valve was normal. There was a persistent left superior vena cava entering a large coronary sinus.

Comment

At the Albany Hospital to date a total of nine cases of atrial septal defect have been diagnosed on the basis of clinical and laboratory findings, including cardiac catheter-

Fig. 3 (Case 3).—Patient with ostium primum defect (right atrial-left ventricular communication) without mitral insufficiency, showing marked cardiac enlargement.

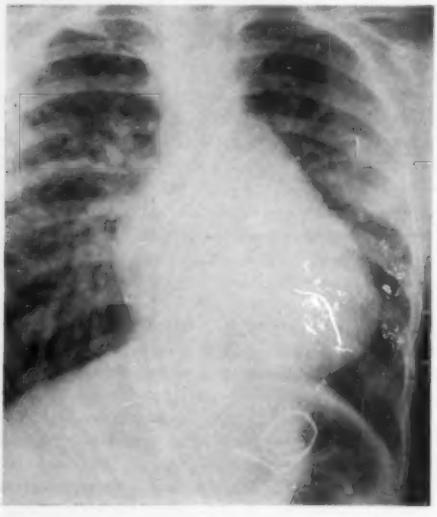


Fig. 4.—Patient with ostium secundum defect without mitral insufficiency, showing smaller-sized heart.

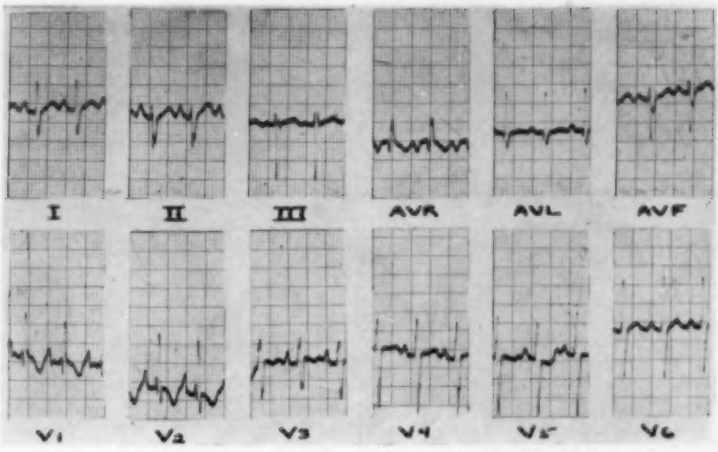
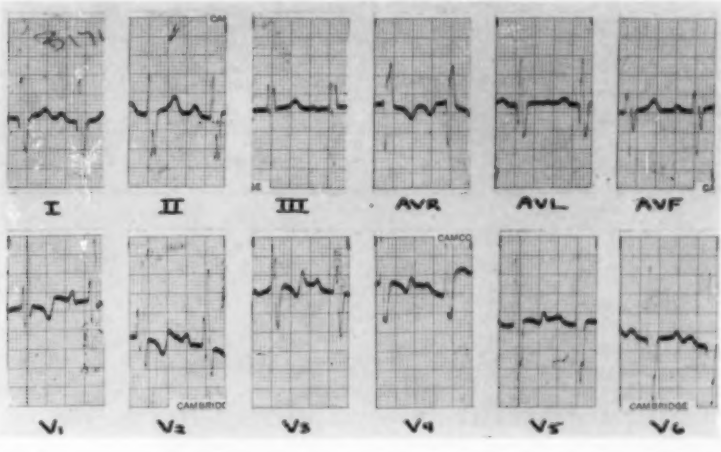


Fig. 5 (Case 1).—Patient with ostium primum defect with mitral insufficiency. Electrocardiogram shows tendency toward left axis and horizontal electrical axis.

ization, and in each case the diagnosis has been confirmed at surgical exploration. Of this number, the three cases outlined above have fallen into the ostium primum group. Of these, Cases 1 and 2 were suspected on the basis of preoperative evaluation. In an attempt to differentiate these three cases a review has been made of the radiographic, electrocardiographic, and clinical findings and catheterization data of the total group.

X-Rays.—In an attempt to correlate cardiac contour and size with the anatomical lesion, the x-rays of the nine cases were presented as unknowns to a radiologist on the staff of the Albany Hospital. He was asked to grade the heart size and vascularity of the lung fields on the basis of 1 to 4. The three ostium primum cases received a rating of 3 to 4, while the secundum defects were graded 1 and 2. No correlation was noted so far as vascularity was concerned. Figures 1 to 3 show x-rays of the three patients with the ostium primum type of defect, and Figure 4, one of the

Fig. 6 (Case 2).—Patient with ostium primum defect with mitral insufficiency. Electrocardiogram shows tendency toward left axis and horizontal electrical axis.



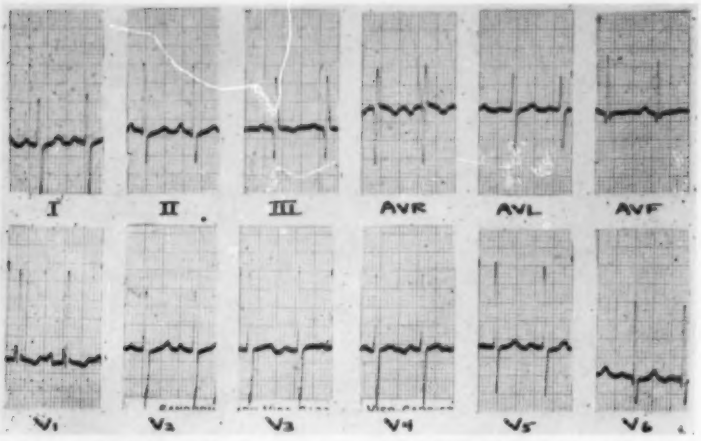
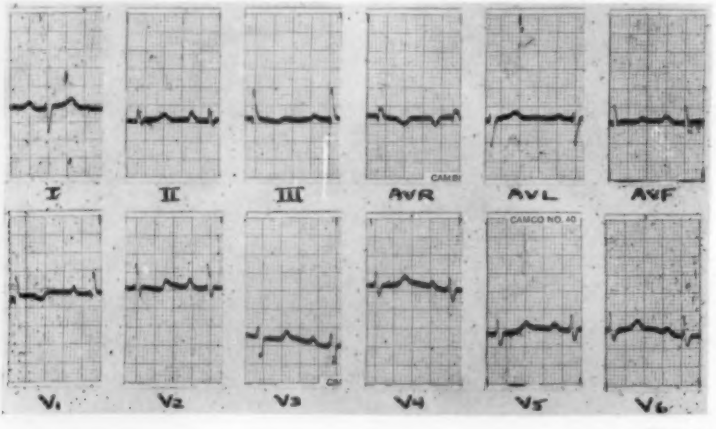


Fig. 7 (Case 3).—Patient with ostium primum defect (right atrial-left ventricular communication) without mitral insufficiency. Electrocardiogram shows right axis and vertical electrical axis.

six patients with secundum type for comparison.

Electrocardiograms.—A review of electrocardiograms showed an incomplete right bundle branch block pattern in all nine cases. Varying degrees of right ventricular hypertrophy were seen in all the ostium primum type cases as well as in some of the secundum defects. In the two cases of ostium primum defect with mitral valve involvement a tendency to left axis and horizontal electrical axis was noted. In the third case, with right atrial-left ventricular communication without mitral valve involvement, a right axis and vertical electrical axis was noted. The other six patients showed a right axis and vertical electrical axis. There was no evidence of left ventricular hypertrophy in the precordial leads, but left axis and horizontal electrical axis is most unusual in our series of atrial septal defects and correlates well with involvement of the mitral valve. Figures 5 and 6 show the electrocardiograms of patients with mitral insufficiency, and Figure 7 shows the electrocardiogram of the patient with

Fig. 8.—Patient with ostium secundum defect without mitral insufficiency. Electrocardiogram shows right axis and vertical electrical axis.



Data Obtained at Cardiac Catheterization

Case	Age	Pressure, Mm. Hg			Oxygen Content, Vol. %					Capacity O_2, Vol. %
		PA *	RV *	RA *	FA *	PA	RV	RA	SVC *	IVC *	
1	27 mo.	30/16	38/3	8/1	14.6	15.5	15.1	14.3	11.2	11	16.6
2	10 yr.		46/4	3	17.1	15.2	13.9	14.3	13.7	10.2	18.7
3	12 yr.	53/46	64/16	15	16.5	14.1	13.4	13.5	10	10.9	17.3
4	13 yr.	35/8	33/4		14.9	14.7	14.0	13.3	10.7	11.5	15.9

* PA, pulmonary artery; RV, right ventricle; RA, right atrium; FA, femoral artery; SVC, superior vena cava; IVC, inferior vena cava.

the right atrial-left ventricular communication without mitral valve involvement. Figure 8 shows the electrocardiogram of the patient with a secundum-type defect whose x-ray was seen in Figure 4.

Clinical Findings.—In general, the degree of physical disability was most marked in the patients with the ostium primum type of defect. Patients 2 and 3 were severely disabled, and Patient 2 was in overt congestive failure when seen in the hospital. Patient 1 was markedly restricted in her activities, and it was difficult to know what her capabilities were. In regard to auscultatory findings in Case 2 there was a typical murmur of mitral insufficiency in addition to a murmur at the pulmonic area. Patient 1 had a loud medium-pitched somewhat harsh murmur radiating well into the axilla, but the findings were not conclusive of mitral insufficiency. Patient 3 had no murmur suggestive of mitral insufficiency, nor did any of the patients with secundum-type defects. Mid-diastolic murmurs were heard in both groups of patients.

Catheterization Data.—A review of the catheterization data failed to disclose any significant differentiating points between the two groups. The catheter was not passed across the defect in any of the cases. The right atrial pressure curves of Case 3 were particularly scrutinized, as one might expect some abnormality of the C and V waves with a right atrial-left ventricular communication and a defect of the tricuspid valve, but except for a prominent A wave none were seen (Table).

Summary

Nine cases of atrial septal defect confirmed by catheterization and later by surgical exploration are reviewed. Of these, three were the ostium primum type of defect, while six were simple secundum defects. A correlation of x-ray, electrocardiographic, clinical, and catheterization data is made. In this series increased heart size, tendency to left axis and horizontal electrical axis, and the presence of a murmur of mitral insufficiency were strongly suggestive of ostium primum type of defect with mitral valve involvement. In the one case of ostium primum type of defect without mitral valve involvement only increased heart size and a marked degree of physical disability were noted.

133 Delaware Ave. (9).

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Electrocardiographic Findings in One Hundred Verified Cases of Ventricular Septal Defect

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We have reviewed the electrocardiograms of 100 children with isolated ventricular septal defect for (1) possible typical or diagnostic patterns, (2) relationship to pulmonary artery pressure and flow and to histological pulmonary vascular changes, and (3) prognostic significance as to surgical risks.

Descriptions regarding the electrocardiogram in patients with ventricular septal defect have been varied. Taussig [1] considered the electrocardiogram to be of little diagnostic aid in ventricular septal defects. She noted that bizarre ventricular complexes of high amplitude were often associated with this defect but stated that similar findings occurred with equal frequency in other heart malformations. Others have reported that the electrocardiogram varies with the clinical picture, depending upon the size of the septal defect, location of the defect, and the pulmonary peripheral resistance. Kjellberg et al.,[2] in reviewing their 45 cases with this defect, noted that when the pulmonary and systemic arterial pressures were balanced the burden on the right ventricle was increased, leading to right ventricular hypertrophy patterns on the electrocardiogram. In cases with a large ventricular septal defect, with both a large left-to-right shunt and increased pulmonary resistance, a pattern of combined ventricular hypertrophy occurred. Nadas [3] recognized two groups: In the small ventricular septal defect, the electrocardiogram was normal in the vast majority of instances, but occasionally left ventricular preponderance was found; in cases where the defect was large, right ventricular hypertrophy alone or in combination with left ventricular hypertrophy was found, often with right bundle branch block (25%), first- or second-degree atrioventricular block (10%), and widening and peaking of the P waves.

Marsico et al.[4] and Sodi-Pallares [5] described two general patterns. If the pressure in the right ventricle is below 60 mm. Hg, there is systolic overloading of the right ventricle and diastolic overloading of the left ventricle (high-voltage R waves in Leads V_1 and V_2; tall, peaked, and symmetrical T waves in Leads V_5 and V_6, often with elevation and upward concavity of the RST segment). If the pressure in the right ventricle is above 60 mm. Hg, then there are deep S waves in Lead V_6, the intrinsicoid deflection is not delayed, and the T waves are normal rather than peaked or tall. These authors also reported left ventricular hypertrophy (tall R wave in Lead V_6, or normal R wave if right ventricular hypertrophy is also present, plus deep Q waves and delayed intrinsicoid deflection), septal hypertrophy (deep Q waves in Leads V_5 and V_6), and large diphasic complexes in the midprecordial leads (Katz-Wachtel sign [6]) as signs of ventricular septal defect. They found no consistent correlation between P wave changes and right atrial or right ventricular pressures.

DuShane et al.[7] found that surgery was tolerated better by patients with electrocardiographic evidence of left ventricular hypertrophy in addition to any right ven-

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tricular hypertrophy that might be present. In a subsequent publication [8] this group reported a close correlation between the electrocardiographic interpretation and intracardiac hemodynamics. If severe pulmonary hypertension existed with balanced or predominant right-to-left shunting of blood, the electrocardiogram exhibited evidence of right ventricular systolic overloading without evidence of increased left ventricular work. If the pulmonary arterial pressure was considerably less than the systemic, there was evidence of left ventricular diastolic overloading and little or no evidence of right ventricular systolic overloading. Those with considerable pulmonary hypertension but a predominant left-to-right shunt showed right ventricular systolic or combined right ventricular overloading, as well as left ventricular diastolic overloading. Hubbard and Angle [9] likewise concluded that the electrocardiogram reflects with reasonable accuracy the type and magnitude of the hemodynamic abnormality. Mannheimer and associates [10] noted left ventricular hypertrophy to be present in cases with lower pressures, and there was right or combined hypertrophy in those with high pressures. On the other hand, Zacharioudakis et al.[11] have recently reported inability to correlate electrocardiographic findings with clinical, hemodynamic, and postmortem findings in 15 cases of ventricular septal defect in infancy. Dreifuss and associates [12] likewise have found a poor correlation of electrocardiographic and hemodynamic data.

Zimmerman and associates [13,14] noted normal electrocardiograms in cases of the Roger type, RSR′ pattern in 60% of those with moderate elevation in right ventricular pressure, right ventricular hypertrophy in cases with further elevation in right ventricular pressures, and flattening of the T waves in the left-sided precordial leads in all patients in whom the pulmonary artery pressure approached the systemic artery pressure. They consider that left ventricular diastolic overloading constitutes a favorable sign and left ventricular systolic overloading, an unfavorable sign, with respect to operative risk. Burchell [15] found the electrocardiogram to be of inestimable help in determining operability, with left ventricular preponderance a favorable sign, but he stated that right ventricular hypertrophy in itself was not an interdiction of surgery.

Material

The electrocardiograms (routine hospital tracings, with standard 12 leads taken with a direct-writing single-channel electrocardiograph) of 100 children with proven isolated ventricular septal defect were studied. All but one had intracardiac surgery, the one exception being a child who died before surgery could be performed. This material does not cover the whole spectrum of ventricular septal defect, inasmuch as surgery was deferred in cases with minimal left-to-right shunts and normal pulmonary artery pressures and cases with predominant right-to-left shunt were considered inoperable. Electrocardiograms were taken shortly prior to surgery.

Intracardiac pressures and pulmonary flow data were obtained at right heart catheterization. The pulmonary vascular changes were determined from lung tissues obtained either by lung biopsy prior to, or coincident with, intracardiac surgery or at autopsy. The lung tissues were examined by Dr. D. C. Ferguson, of the Veterans' Administration Hospital, Minneapolis. The tissues were stained with the Verhoef-Van Gieson elastic tissue stain. The degree of vascular change was graded as follows: medial hypertrophy of small pulmonary vessels alone, Grade 1; moderate intimal proliferation, Grade 2, and severe intimal proliferation, Grade 3. The details of this grading system are being reported elsewhere.[16]

We are including all of the basic measurements in the Appendix to this paper in order that others may be able to apply their own methods of analysis and interpretation. Standard criteria for the determination of ventricular hypertrophy have yet to be established for the pediatric range. We have tried to obviate this problem by comparing our scalar measurements with those published for normal children of various ages by Ziegler,[17] thereby obtaining ratio values. Such ratios permit the comparison of mixed age data, though certain bias is thereby introduced (e. g., ratios based on low medians will exaggerate the absolute value). These ratios have been used in testing for correlations with physiological and pathological findings. In addition, we have analyzed the individual electrocardiograms for evidence of hypertrophy by the

conventional methods and also by the system of overloading patterns described by the Mexican group.

Results from Ratio Analyses

1. *Right Ventricular Preponderance.*—One criterion for right ventricular hypertrophy (or preponderance) has been the ratio of the amplitude of the R wave in Lead V_1 to the amplitude of the sum of the R and S waves in this lead. A value higher than "normal" is said to indicate right ventricular hypertrophy, though no one has determined the limits of "normal." We have compared the individual R/RS ratios in Lead V_1 with the R/RS ratios listed by Ziegler[17] for the various age groups. A ratio of 1.0 is obtained when the individual ratio is the same as the median value given by Ziegler, and a ratio of 2.0, when the ratio is double this value. Right ventricular hypertrophy can then be designated at whatever level above the normal that the particular investigator considers to be correct, but all patients are compared to a relatively uniform standard of reference. When such values are plotted against the pulmonary systolic pressures in a scattergram (Fig. 1), it is apparent that with increase in pressure there is a slight increase in the average of the ratio obtained (increasing ratio indicates increasing right ventricular hypertrophy or preponderance) but much scattering of values. There is only a slight correlation between these values and patient survival (black dots on scattergram indicate deaths). These data are shown also in simplified tabular form (Table 1), where the slight but definite correlation of pulmonary pressure with right ventricular preponderance and with surgical death is more easily identified.

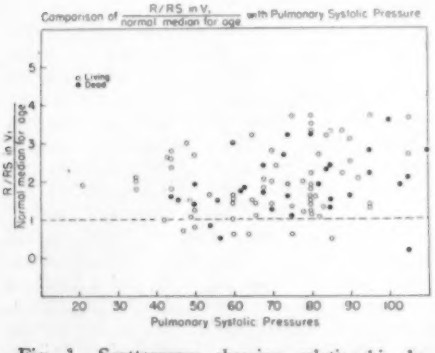

Fig. 1.—Scattergram showing relationship between pulmonary artery systolic pressures and relative values of R/RS percentage in Lead V_1.

TABLE 1

Cases No.	Pulmonary Systolic Pressure Mm. Hg.	Living	Dead	Average of Individual Ratios of R/RS in V_1 Median
21	20-50	17	4	1.7
26	51-70	17	9	1.6
40	71-90	29	11	2.1
12	91-111	5	7	2.2

2. *Isolated or Combined Ventricular Hypertrophy.*—In determining the presence of right, left, or combined ventricular hypertrophy, the QRS complexes in Leads V_1 and V_6 in each individual case were measured. Each value of the complex was compared to the median value for age (after Ziegler), and a ratio was thereby obtained. We have arbitrarily used a ratio of 1.5 as that point above which hypertrophy was deemed to be present. Where two values were used in a single calculation, a ratio of 3.0 was considered to be the comparable upper limit of normal.

In evaluating relative ventricular hypertrophy, three different methods were used:

(1) $\frac{R}{\text{median}}$ in V_6 was plotted against $\frac{R}{\text{median}}$ in V_6

(2) $\frac{R}{\text{median}}$ in $V_1 + \frac{R/RS}{\text{median}}$ in V_1 was plotted against $\frac{R}{\text{median}}$ in $V_6 + \frac{R/RS}{\text{median}}$ in V_6

(3) $\frac{R}{\text{median}}$ in $V_1 + \frac{S}{\text{median}}$ in V_1 was plotted against $\frac{R}{\text{median}}$ in $V_6 + \frac{S}{\text{median}}$ in V_1

The scattergram obtained by using Method 2 is shown in Figure 2. Cases having right ventricular hypertrophy fall in the upper left quadrant; those with combined ventricular hypertrophy, in the upper right; those with left ventricular hypertrophy, in the lower right, and those without hypertrophy,

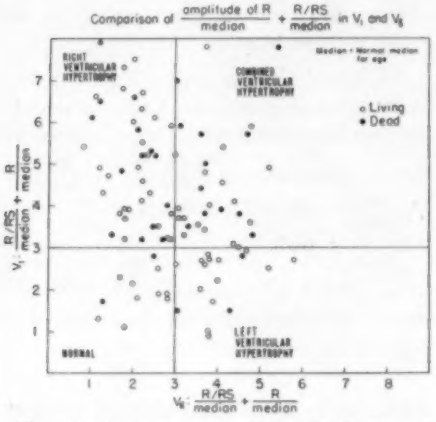
Comparison of amplitude of R / median + R/RS / median in V1 and V6
RIGHT VENTRICULAR HYPERTROPHY
COMBINED VENTRICULAR HYPERTROPHY
LEFT VENTRICULAR HYPERTROPHY
NORMAL
Living
Dead
V1 R/RS / median + R / median
V6 R/RS / median + R / median

Fig. 2.—Scattergram to show distribution of cases with regard to type of ventricular hypertrophy present.

ble relationship between pulmonary flow (and hence the amount of left to right shunt) and T wave voltage, these two factors have been plotted on a scattergram (Fig. 3). There is no apparent correlation, but survival was higher in those with T waves greater than the median (14 in 20) than in those with T waves less than the median (17 in 32).

Relationship of Right Ventricular Hypertrophy to Pulmonary Vascular Changes.—This relationship was studied by plotting the earlier-described $\frac{R/RS}{median}$ in V_1 values against the degree of lung change. This is illustrated in Figure 4. No significant correlation was found, but it is interesting to

TABLE 2

	$\frac{R \text{ in } V_1}{\text{Median}}$ Compared with $\frac{R \text{ in } V_6}{\text{Median}}$	$\frac{R + R/RS \text{ in } V_1}{\text{Median}}$ Compared with $\frac{R + R/RS \text{ in } V_6}{\text{Median}}$	$\frac{R \text{ in } V_1 + S \text{ in } V_6}{\text{Median}}$ Compared with $\frac{R \text{ in } V_6 + S \text{ in } V_1}{\text{Median}}$
Right ventricular hypertrophy	18 living 7 dead	30 living 14 dead	40 living 15 dead
Combined ventricular hypertrophy	21 living 20 dead	16 living 11 dead	20 living 8 dead
Left ventricular hypertrophy	26 living 2 dead	14 living 3 dead	3 living 4 dead
No hypertrophy	5 living 1 dead	10 living 2 dead	8 living 2 dead

in the lower left. Deaths are indicated by solid circles. As shown in Table 2, Methods 1 and 2 both indicated a lower mortality for cases with either left or no ventricular hypertrophy, while Method 3 showed no difference of note. However, these three different methods of identifying ventricular hypertrophy gave considerable variation in the number of cases falling into the various categories.

Relationship of Voltage of T in V_6 to Pulmonary Flow.—In the concept of diastolic overloading of the left ventricle, the T wave configuration is considered to be the most important feature. To test for possi-

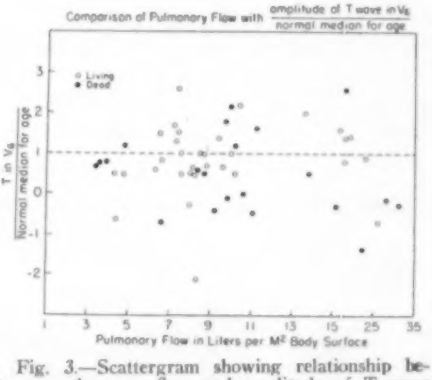
Comparison of Pulmonary Flow with amplitude of T wave in V6 / normal median for age
Living
Dead
T in V6 / Normal median for age
Pulmonary Flow in Liters per M2 Body Surface

Fig. 3.—Scattergram showing relationship between pulmonary flow and amplitude of T wave in Lead V_6.

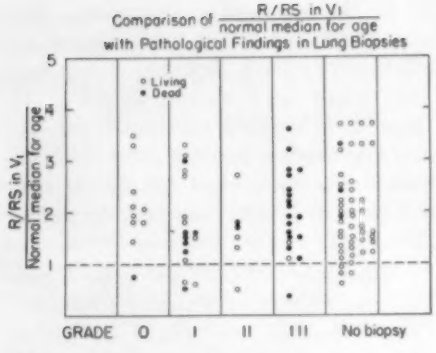

Fig. 4.—Scattergram to show relationship between pulmonary histological findings and relative values of R/RS percentage in Lead V_1.

note the high incidence of surgical death in cases with Grade 3 changes, an observation already noted by Adams et al.[16]

Relationship of T Wave Voltage in V_6 to Lung Pathology and Survival.—The height of the T wave in Lead V_6 was compared with the median for age. If this ratio was greater than 1.5, the T was termed "high"; if between 1.0 and 1.5, as "upper normal"; if between 0 and 1.0, as "low normal," and separate categories were made for diphasic and inverted T waves. This comparison is shown in Table 3. No significant correlation was found with lung pathology, but again survival was higher in those with upright T waves. Lung biopsies were performed primarily in cases where severe pulmonary hypertension was present, and this undoubtedly accounts for the low mortality in the group without biopsies.

Additional Comparisons Using Ratios.—We have used these ratio values in searching for other relationships also. These included comparisons of $\frac{R/RS}{median}$ in V_6, $\frac{R/RS}{median}$ in V_1, $\frac{R}{median}$ in V_6, $\frac{R}{median}$ in V_1, and $\frac{P}{median}$ in II with lung pathology and comparisons of $\frac{T}{median}$ in V_6 and $\frac{T}{median}$ in V_1 with pulmonary pressure. None of these showed an appreciable correlation.

Analyses by More Conventional Methods and Overloading Patterns

Definitions: As criteria for right ventricular hypertrophy we have used the following:

(1) Voltage of R or R′ in V_1 greater than 99th percentile for R (data of Ziegler[17])

(2) Ratio of R/RS in V_1 greater than the 99th percentile

(3) Voltage of T wave in V_1 greater than the 99th percentile

For identifying left ventricular hypertrophy, we have used the following:

(1) Voltage of R in V_6 greater than the 99th percentile; if no q is present in V_6, then the voltage of R in AVF is used.

For identifying combined or relative ventricular hypertrophy we have used the following:

TABLE 3.—*Comparison of T Wave Voltage in V_6 with Pulmonary Pathology*

T Wave Voltage	Pulmonary Pathology					
	Grade 0	Grade 1	Grade 2	Grade 3	No Biopsy	Totals
High	--	2 L	2 L 1 D	3 D	12 L	16 L 4 D
Upper normal	2 L	5 L 2 D	1 L	3 D	14 L 1 D	22 L 6 D
Lower normal	4 L 1 D	4 L 1 D	--	2 L 7 D	13 L 2 D	23 L 11 D
Diphasic	--	--	-- 1 D	1 D	1 L	1 L 2 D
Inverted	3 L	1 L 4 D	1 L	4 D	4 L	9 L 8 D
Totals	9 L 1 D	10 L 7 D	4 L 2 D	2 L 18 D	44 L 3 D	69 L 31 D

(1) The R wave voltages as defined above

(2) The ratio of $\frac{(R_8+S_1)/(R_1+S_8)}{\text{median for age}}$. These values have been lumped together to give "average preponderance" values for each group (the lower the value, the greater the relative right ventricular preponderance).

The use of overloading pattern terminology has been developed by the Mexican group.[4,5,15,19] However, nowhere have we found strict criteria for their recognition, particularly in the pediatric age range. The general criteria listed originally by the Mexican group [15] are as follows:

Right ventricular systolic overloading (RVSO): increased voltage of R in V_1, sometimes with initial slurring; negative T waves may be present in Lead V_1.

Right ventricular diastolic overloading (RVDO): complete or incomplete right bundle branch block.

Left ventricular systolic overloading (LVSO): negative T waves and/or ST segment in the "left ventricular" leads.

Left ventricular diastolic overloading (LVDO): high delayed R wave in V_5 and V_6 with deep S waves in V_2 and V_3 and, especially, a high positive T wave in V_5 and V_6.

DuShane and associates [8] have found overloading terminology to be very useful and have changed the criteria slightly. DuShane lists the identifying features of right ventricular systolic overloading as R, Rs, or qR patterns in V_1, with sharply inverted T, or with upright T waves in infancy and early childhood; right ventricular diastolic overloading is characterized by RSR′, RSr′, or rSr′ complexes in V_1; left ventricular systolic overloading is featured by V_5 and V_6 leads showing a q wave followed by tall broad R waves with the intrinsicoid deflection greater than 0.04 second and associated with flattened or inverted T waves, and left ventricular diastolic overloading is identified in Leads 2, 3, aV_F, and V_6 by deep q waves, tall R waves and tall, peaked, upright T waves, the peaked T waves being the most significant.

Other workers, such as Nadas [3] and Grant et al.,[20] point out objections to the use of "overloading" terminology. It must be stated that both Sodi-Pallares [5] and DuShane [8] acknowledge that this method of terminology may not be strictly or technically correct, even though they consider this method of analysis to be of great clinical value.

In general, T wave contour has been considered the central feature of left ventricular overloading patterns, with peaked T waves indicating diastolic overloading and flat or negative T waves indicating systolic overloading. By definition, then, left ventricular systolic and diastolic overloading do not occur simultaneously. On the other hand, since increased R wave voltage has been the primary sign of RS, and a right bundle branch block, the primary sign of RD, right ventricular systolic and diastolic overloading may occur together.

We have attempted to define these patterns in exact terms, so that we could make an objective analysis (knowing, of course, that dissecting an electrocardiogram for special features may result in the loss of the "gestalt" value). We have, therefore, characterized the various overloading patterns as follows:

(1) RVSO: Voltage of R or R′ in V_1 greater than the 99th percentile (normal values of Ziegler [17]) (This is, then, the same criterion as the one already described for RVH)

(2) RVDO: Complete or incomplete right bundle branch block

(3) LVSO: A qR(s) pattern in V_6 (or aV_F if there is no q in V_6), with the R wave above the 75th percentile, followed by a T wave below the 1% percentile

(4) LVDO: A qR(s) pattern in V_6 (or aV_F if there is no q in V_6), with the R wave above the 75th percentile in voltage, followed by a T wave above the 99th percentile

Results

The data obtained by these analyses are shown in Table 4.

With a few exceptions, we have been unable to identify any strong correlations of hypertrophy or overloading patterns with pulmonary flow, pulmonary pressure, pulmonary pathology, surgical mortality, or age. General findings are the following.

TABLE 4.—*Analyses by Conventional*

Category	Cases, No.	RVH, %R/RS in V_1	Av. Prep.	Voltage			High T′ in V_1	Deep Q′ in V_6	Prolonged Intrinsicoid	
				RVH Only	LVH Only	Combined VH			V_1	V_6
Plumonary flow, L/sq. m/m.	6									
4- 5.9	6	4	0.45	3	1	0	4	1	5	0
6- 8.9	23	18	0.83	7	6	6	7	7	20	1
9-11.9	19	14	0.48	4	11	2	5	4	13	3
12-	19	10	0.83	2	11	4	6	4	18	7
Pulmonary artery systolic Pressure, mm. Hg.										
20-50	20	14	0.96	2	10	4	5	3	16	1
51-80	50	32	0.71	14	25	9	13	10	41	6
81-	29	23	0.48	9	8	6	14	6	24	3
Pressure over 80										
Flow over 9	13	10	0.63	2	4	4	4	3	11	2
Flow under 9	10	8	0.33	5	1	2	7	2	7	0
Pressure under 50										
Flow over 9	6	4	1.0	0	4	1	2	1	6	0
Flow under 9	6	5	0.73	1	2	1	1	0	6	0
Lung pathology										
Grade 0	10	8	0.89	4	4	0	2	5	8	1
Grade 1	17	10	0.85	4	7	3	5	2	15	0
Grade 2	6	4	0.87	2	4	0	2	3	4	1
Grade 3	20	13	0.50	7	6	5	11	2	19	3
Present status										
Living	69	46	0.74	15	33	11	17	25	56	7
Dead	31	23	0.60	10	11	8	15	3	28	3
Age, yr.										
Under 2	30	21	0.64	8	18	9	13	8	29	3
3-5	27	18	0.66	6	14	5	8	9	23	2
6 or over	34	30	0.49	12	13	9	11	10	32	5

Pulmonary Flow.—There is a slight tendency to right ventricular hypertrophy in cases with low flow and to left ventricular hypertrophy in cases with high flow. RVSO was commoner with the low flows, and LVSO, with high flows. Diastolic overloading patterns were equally distributed in all groups.

Pulmonary Pressure.—There was a similar slight tendency for right ventricular hypertrophy to be present with high pressures and left ventricular hypertrophy to be present with low pressures. The "average preponderance" showed a clear-cut change to the right with increasing pressure, though there was a completely overlapping range of individual values in the two groups. RVSO patterns were slightly commoner with high pressures, but it and the other overloading patterns were of little discriminatory help.

Pulmonary Pathology.—Right ventricular hypertrophy and RVSO were slightly commoner in cases with severe pulmonary changes, and the average preponderance was considerably lower (more right) in the group with Grade 3 changes. Left ventricular hypertrophy and other overloading patterns showed no significant trends.

Mortality.—Right ventricular hypertrophy, by all methods, and LVSO were slightly commoner in the surgical death group, and left ventricular hypertrophy, in the living group.

Age.—Right ventricular hypertrophy and RVSO were seen more frequently with increasing age, while LVDO (total of nine cases) was seen only in children 5 years old or younger.

Exceptions.—One of the features included in the descriptions of LVDO is the presence of a q wave in Lead V_6. We have included a separate column for deep q waves in V_6 (greater than the 99th percentile) in Table 4, where one can see that its presence is correlated directly with surgical success. The 3 cases with deep q waves who died all showed right or combined ventricu-

Methods and by Overloading Patterns

Specific Overloading Patterns											Combined Incidence of Individual Components			
RVSO	RVDO	LVSO	LVDO	RVSO RVDO	RVSO LVSO	RVSO LVDO	RVDO LVSO	RVDO LVDO	RVSO RVDO LVSO	None	RVSO	RVDO	LVSO	LVDO
3	1	0	0	0	0	0	0	0	0	2	3	1	0	0
8	5	0	2	4	0	0	1	0	1	2	13	11	2	2
3	1	3	0	3	0	0	0	1	0	8	6	5	3	1
0	2	3	0	1	2	1	1	1	2	6	6	7	8	2
3	2	2	0	3	0	0	1	0	0	9	6	6	3	0
11	5	6	2	7	2	1	1	4	2	9	23	19	11	7
7	3	1	0	4	0	2	0	0	2	10	15	9	3	2
0	1	1	0	4	0	1	0	0	1	6	4	4	1	1
6	2	0	0	1	0	0	0	0	1	1	7	4	1	0
0	0	1	0	1	0	0	1	0	0	3	1	2	2	0
1	2	0	0	1	0	0	0	0	0	2	2	3	0	0
2	1	0	0	0	1	0	1	0	1	4	4	3	3	0
3	3	1	0	3	0	0	1	1	1	4	7	9	3	1
0	0	0	0	1	1	0	0	2	0	2	2	3	1	2
6	1	4	0	3	0	1	0	0	2	3	12	6	6	1
12	10	4	2	10	1	2	1	3	1	23	26	25	7	7
9	1	5	0	4	1	1	1	1	3	5	18	10	10	2
8	3	4	2	4	1	1	1	3	2	10	16	13	8	6
5	5	2	0	4	0	2	0	1	0	8	11	10	2	3
8	3	3	0	6	1	0	1	0	2	10	17	11	7	0

lar hypertrophy, as compared with only 9 of the 25 living cases.

The presence of a T wave above the 99th percentile in Lead V_1 shows a moderate correlation with surgical death. On the other hand, the presence of isolated RVDO appears to be a favorable prognostic sign. The T wave significance is demonstrated in Table 5.

Miscellaneous Observations

Katz-Wachtel Phenomenon.[6]—This feature of diphasic high-voltage QRS complexes in Leads V_2-V_6, was seen in 72% of our cases and showed a somewhat higher incidence in the living group.

TABLE 5

T Wave Characteristics	Status of Patient	
	Living	Dead
0 to + in V_1	17	17
Negative in V_1	52	14
0 to negative in V_1	10	8
Positive in V_1	59	23
0 to + in V_1 & 0 to negative in V_1	2	8
Negative in V_1 & positive in V_1	67	23

Left Axis Deviation.—An axis between 0 and −180 degrees was seen in 16 cases, and, of these, 7 showed a prolonged P-R interval. Three of the latter also showed right ventricular hypertrophy (by voltage), a triad often seen with ostium primum defects.[21,22] No cases showed left axis, prolonged P-R, and right bundle branch block pattern.

Miscellaneous.—A prolonged P-R interval was seen in 22 cases. Peaked P waves were encountered in 16, and 5 showed notched P waves. A qR pattern in V_1 was seen in five cases; only one of these showed an associated prolonged P-R interval, a combination frequently seen in corrected transposition of the great vessels[23] (but this case differed in having inverted T waves in the left precordial leads). Other V_1 patterns were Rs (38%), rsR′ (35%), and R

(22%). A prolonged intrinsicoid in V_1 was present in 84 cases, and a prolonged intrinsicoid in V_6, in only 10.

A negative T wave in V_1 has been considered to be indicative of RVSO, but our data would suggest the reverse. Of our 100 cases, only 10 had R waves in V_1 which were below the 25th percentile, and only 2, below the 1st percentile. On the other hand, 32% had R waves in this lead which were above the 99th percentile.

Even by modifying the definition of LVDO such that any T wave in V_6 over the 75th percentile would be classed as tall and peaked, only 12 additional cases could be added to the original 9 with LVDO.

Conclusions

We began this study with the hope of being able to identify electrocardiographic criteria of prognostic value regarding surgical risks in ventricular septal defect. Our material excludes the two ends of the ventricular septal defect spectrum and hence is not strictly comparable to other studies of this defect. It is to be expected that the two ends—the near-normals and the right-to-left shunts—would differ considerably. On the other hand, the large middle group is the one which concerns the surgeon at the present time.

The reports of others suggest great usefulness of the electrocardiogram in evaluating physiological states and operability, using either conventional criteria or overloading terminology. In contrast, we have found only slight correlations between electrocardiographic values and physiological and histological data. We have found the concept of overloading to be of minimal practical value in identifying flow and pressure data in this range of patients.

Of the many features investigated, only two appeared to have prognostic value. The presence of a deeper than normal q in V_6 appears to indicate a good surgical prognosis, particularly if no right ventricular hypertrophy is present. The presence of a higher than normal T wave in V_1, on the other hand, suggests a poorer prognosis, particularly when coupled with a lower than normal T wave in V_6. The presence of isolated right ventricular diastolic overloading appears to be favorable. Surgical mortality is not just a matter of case severity, and therefore we would not expect to find an infallible prognostic sign.

We have found the electrocardiograms of patients with ventricular septal defect to be extremely variable, and we find it impossible to formulate a typical pattern.

Summary

The electrocardiograms of 100 children with proven isolated ventricular septal defect are analyzed, and the individual scalar values are tabulated. Analyses have been made with use of a system of ratio values, to allow comparisons of mixed-age data, as well as conventional methods and overloading patterns. Correlations have been sought with pulmonary artery pressures and pulmonary flow, histological pulmonary vascular changes, and surgical survival. All but one of the children had intracardiac surgery performed.

No typical patterns have been recognized, but right ventricular hypertrophy was present in the majority of cases and the T waves in Lead V_1 were generally higher than normal. On the whole, there were no strong correlations between electrocardiographic patterns and physiological data. There was some association of right ventricular hypertrophy with increased pulmonary artery pressure and with pulmonary vascular changes. Right ventricular hypertrophy tended to occur with low pulmonary blood flow and high pulmonary artery pressure, and left ventricular hypertrophy, with high flow and low pressure. Right ventricular hypertrophy was commoner among older patients.

The Katz-Wachtel sign was present in 72% of the cases; left axis deviation, in 16%, and a prolonged P-R interval, in 22%. In this series, the presence of deep q waves and upright T waves in V_6 appeared to indi-

cate a good prognosis for surgery, and a higher than normal T wave in V_1 and a lower than normal T wave in V_6, a poor prognosis. The use of overloading criteria was not particularly helpful in evaluating the hemodynamic status of the individual patient. Left ventricular diastolic overloading was present in only 9% of the cases.

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Appendix

Individual ECG Measurements

				Lead 2			Lead aV$_F$				Lead V$_1$				Lead V$_5$			Lead V$_6$			T Wave						
Case	Age	Axis	Rate	P-R	QRS	Q-T	Q	R	S	Pattern	Q	R	S	In. Def.	R	S	Q	R	S	In. Def.	aV$_F$	V$_1$	V$_6$	Pul. Art. Sys. Pr.	Lung Grade	Status L or D	Pul. Flow Sq. M.	Case
1	2 mo.	70	150	0.12	0.04	0.22	2	10	1	R	0	10	0	0.04	36	35	2	16	2	0.03	4	−2	2.5	44	1	D	4.9	1
2	2	80	154	0.10	0.08	0.24	5	30	4	rsR′	0	35	4	0.05	40	16	2	35	14	0.03	2	1	−1	56	3	D	15.6	2
3	3	60	116	0.12	0.06	0.28	5	25	2	RS	0	30	10	0.04	44	30	3	34	2	0.03	5	−1	3	60	1	D	10.9	3
4	4	90	150	0.16	0.06	0.24	0	12	1	qR	14	22	0	0.04	24	20	0	40	30	0.02	2	di	−2	50	1	D	6.7	4
5	4	80	160	0.12	0.04	0.24	5	20	0	qR	2	15	0	0.02	60	30	0	30	18	0.02	2.5	−2	6	54	—	L	10.6	5
6	4	90	130	0.16	0.06	0.20	1	10	2	rsR′	0	21	2	0.04	50	30	0	27	10	0.02	4	1	1	80	—	L	—	6
7	4	85	158	0.12	0.09	0.26	2	15	1	Rs	0	22	1	0.04	40	40	4	22	20	0.03	4	−4	4	49	—	L	—	7
8	4	45	132	0.10	0.04	0.24	1	21	3	rsR′	0	19	8	0.05	40	18	0	50	20	0.04	4	−3	8	80	—	L	36.6	8
9	6	120	180	0.10	0.05	0.24	0	5	1	rsR′	0	24	2	0.04	40	20	3	28	12	0.03	2	2	−0.5	90	1	D	28.2	9
10	8	90	120	0.14	0.06	0.28	4	15	2	rsR′	0	7	5	0.04	18	20	3	19	16	0.02	3.5	−4	4	82	1	L	17.5	10
11	8	70	160	0.12	0.06	0.28	3	13	2	R	0	15	0	0.03	30	16	1	24	6	0.02	2	di	−1	62	3	D	31.8	11
12	8	70	140	0.10	0.07	0.28	4	15	4	rsR′	0	22	4	0.04	25	10	5	28	6	0.04	4	−3	5	60	—	L	—	12
13	9	−30	140	0.16	0.07	0.22	0	4	7	Rs	0	5	1	0.05	68	20	3	23	5	0.03	2.5	−1	3.5	60	0	L	19.1	13
14	10	−48	180	0.12	0.05	0.22	0	7	9	RS	0	25	17	0.03	40	60	4	13	6	0.03	3.6	−1	2	66	1	L	8.6	14
15	11	105	172	0.12	0.06	0.28	8	28	2	RS	0	71	11	0.02	46	40	2	25	13	0.03	3	1	−0.5	50	—	L	—	15
16	11	90	160	0.13	0.04	0.22	1	12	4	RS	0	11	26	0.02	24	40	3	26	0	0.03	1.5	2	−1.2	56	1	D	9.2	16
17	11	85	180	0.12	0.07	0.24	2	10	0	rsR′	0	32	3	0.06	25	8	6	32	7	0.03	3	−1	5	60	—	L	7.4	17
18	12	75	150	0.12	0.08	0.26	8	25	0	qR	4	15	0	0.03	30	40	0	34	10	0.02	5	−1	6	60	—	L	7.1	18
19	12	80	130	0.12	0.06	0.24	2	13	3	rsR′	0	10	5	0.04	30	40	6	50	6	0.03	3.5	−3	2	70	—	L	4.3	19
20	12	60	160	0.12	0.04	0.24	5	15	0	Rs	0	34	2	0.03	40	30	4	15	0	0.04	3	−2	3	44	0	L	—	20
21	12	30	130	0.16	0.06	0.26	0	23	19	rsR′	0	6	5	0.06	30	40	0	10	12	0.02	3.2	−3	6	75	3	D	—	21
22	13	85	120	0.11	0.05	0.28	1	12	1	rsR′	0	28	6	0.05	28	4	4	40	6	0.02	3.8	−2	3.5	40	—	L	—	22
23	14	80	125	0.11	0.07	0.30	0	7	5	R	0	10	0	0.04	25	20	5	12	5	0.03	4	−5	4	35	—	L	—	23
24	14	100	160	0.16	0.06	0.20	0	7	8	Rs	0	28	5	0.02	55	50	5	16	2	0.03	2.5	−3	−2	68	0	L	25.7	24
25	14	70	140	0.14	0.06	0.28	6	15	10	rsR′	0	12	4	0.05	20	3	1	45	25	0.03	3	−2	−3	46	1	D	—	25
26	17	90	140	0.12	0.07	0.28	7	25	0	RS	0	23	10	0.02	30	40	2.5	13	3	0.03	4.5	−1.5	2.5	95	—	L	6.4	26
27	18	90	150	0.11	0.05	0.24	3	19	4	Rs	0	6	4	0.02	16	30	0	16	8	0.02	5	−0.5	2.2	65	—	L	7.3	27
28	20	−20	160	0.14	0.06	0.26	0	10	7	RS	0	40	60	0.02	30	40	3	20	0	0.05	1	4	1.5	54	0	D	—	28
29	2 yr.	100	160	0.14	0.06	0.28	2	11	0	Rs	0	9	1	0.03	45	32	5	30	10	0.03	3	−2	−3	35	—	L	—	29
30	2	−140	140	0.12	0.08	0.28	2	15	3	R	0	29	0	0.07	34	50	12	44	20	0.03	4	−12	8	80	—	L	—	30
31	2	−30	160	0.11	0.06	0.28	0	9	10	rS	0	8	16	0.09	12	20	4	11	0	0.03	5	−2	1.5	42	—	L	—	31
32	2	70	145	0.12	0.08	0.28	4	25	4	Rs	0	9	4	0.04	40	20	10	36	8	0.04	4	−2	2.8	80	—	L	23.6	32
33	2	80	148	0.12	0.07	0.28	2	26	0	RS	0	34	20	0.02	20	10	3	32	0	0.03	3	di	2.5	82	3	D	8.3	33
34	2	90	140	0.12	0.06	0.28	3	21	1	Rs	0	14	2	0.03	40	44	0	20	15	0.02	2	−1	2	50	—	D	—	34
35	2	60	115	0.13	0.09	0.31	3	12	5	rsR′	0	13	4	0.05	60	28	10	47	10	0.04	5	−3.5	7.5	80	2	L	—	35
36	2	100	130	0.14	0.06	0.28	5	28	8	rsR′	0	15	3	0.05	60	40	2	50	30	0.03	3	−5	7	68	2	D	10.6	36
37	2	105	160	0.12	0.08	0.32	2	23	0	qRs	1	12	7	0.02	30	30	0	26	6	0.03	4	1	−2	83	2	L	4.5	37
38	2	80	117	0.14	0.07	0.29	1	17	3	rS	0	3	7	0.03	40	30	1	35	8	0.02	5.5	−5	5	47	1	L	16.5	38
39	2	180	170	0.14	0.08	0.24	0	13	12	R	0	15	0	0.06	50	22	5	12	6	0.03	6	−1.5	2	92	0	L	9.0	39
40	3	130	134	0.12	0.08	0.28	2	15	3	rSR′	0	24	12	0.05	36	48	1	18	9	0.03	9	−5	5	60	—	L	—	40
41	3	70	120	0.16	0.08	0.32	0	20	12	R	0	18	0	0.05	34	32	11	52	10	0.05	6	−5	6	68	—	L	7.4	41
42	3	150	124	0.20	0.08	0.28	0	19	3	rSR′	0	25	4	0.06	30	40	5	36	16	0.04	3.5	−3	4	82	3	D	—	42
43	3	90	120	0.16	0.06	0.28	1	17	6	rsR′	0	16	3	0.04	30	45	6	26	4	0.04	6	−2	2.5	80	1	L	9.6	43

44	3	55	120	0.13	0.06	0.28	0	18	6	rSr′	0	2	7	0.04	20	18	5	25	2	0.04	7	−6	7	64	1	L	—	44
45	3	100	120	0.14	0.06	0.24	3	32	7	Rs	0	15	1	0.06	44	30	5	20	4	0.04	4	−2	3	68	0	L	6.6	45
46	3	−60	134	0.16	0.08	0.30	0	15	10	RS	0	18	15	0.04	30	36	4	20	4	0.03	6	d1	6	78	—	L	—	46
47	3	100	130	0.16	0.08	0.30	3	25	4	R	0	19	0	0.06	20	48	1	8	8	0.03	3	−2	2	78	—	L	7.5	47
48	3	0	124	0.14	0.08	0.32	0	15	15	RS	0	15	13	0.04	30	40	4	44	12	0.03	5.5	1	5	50	—	L	—	48
49	3	100	130	0.13	0.06	0.28	4	22	3	rSr	0	3	8	0.03	24	46	0	8	10	0.03	3.2	−5	−1.5	—	—	L	—	49
50	3	70	155	0.10	0.04	0.18	1	20	3	RS	0	20	40	0.04	40	30	0	40	40	0.03	3	d1	−5	75	—	L	—	50
51	4	110	116	0.14	0.08	0.36	2	14	3	Rs	0	4	2	0.02	—	—	5	32	18	0.03	4	−1	5	75	—	L	—	51
52	4	110	150	0.12	0.08	0.28	0	11	13	rsR′	0	28	4	0.03	30	14	0	22	22	0.03	5	−4	4	103	3	D	9.8	52
53	4	150	120	0.14	0.06	0.36	0	15	4	Rs	0	38	2	0.04	40	50	4	56	18	0.03	3	−2	10	105	3	D	18.4	53
54	4	−60	100	0.20	0.08	0.30	0	7	17	Rs	0	15	6	0.04	45	30	4	36	13	0.04	6.5	5	d1	74	3	D	10.6	54
55	4	165	104	0.16	0.07	0.28	1	7	7	R	0	34	0	0.03	35	15	1	11	8	0.04	4.5	2	3	95	3	D	4.0	55
56	4	120	148	0.12	0.07	0.24	2	5	2	rsR′	0	27	4	0.06	20	20	0	20	30	0.03	6	−2	−8	74	1	L	8.2	56
57	4	−30	120	0.20	0.08	0.30	4	12	3	Rs	0	15	8	0.03	34	24	3	24	24	0.03	4.5	2.5	5	75	—	L	—	57
58	5	−20	140	0.14	0.06	0.32	0	9	14	RS	0	9	10	0.04	24	40	1.5	6	1	0.03	3.4	d1	1.8	49	3	L	10.1	58
59	5	80	150	0.14	0.07	0.28	0	30	10	Rsr′	0	7	2	0.02	50	40	2	50	2	0.04	7	d1	4	80	—	L	—	59
60	5	110	140	0.14	0.07	0.24	1	20	4	Rs	0	7	1	0.03	5	30	0	20	30	0.03	2	−2	6.5	85	3	D	11.9	60
61	5	30	130	0.15	0.06	0.26	1	18	4	rsR′	0	4	5	0.02	20	30	4	30	10	0.03	3.5	−2	5.5	82	1	L	9.4	61
62	5	−5	100	0.12	0.08	0.32	0	10	14	Rs	0	6	4	0.02	20	30	7	40	0	0.06	6	1.5	−1.5	70	—	L	—	62
63	5	70	110	0.13	0.08	0.28	0	12	14	rsR′	0	5	1	0.06	10	12	3	36	6	0.03	3	−1.5	4	40	—	L	8.5	63
64	5	90	120	0.12	0.08	0.28	0	9	2	R	0	15	0	0.05	34	34	5	34	2	0.04	5.5	−4	3	48	—	L	—	64
65	5	70	110	0.16	0.08	0.36	2	26	9	Rs	0	25	7	0.04	60	60	10	40	4	0.04	8	−3	8	90	—	L	13.7	65
66	5	100	100	0.12	0.08	0.34	2	22	1	rsR′	0	5	2	0.04	10	30	1.5	23	1	0.03	5	−2	6	44	—	L	6.5	66
67	6	0	90	0.16	0.06	0.36	0	9	6	R	0	10	0	0.05	24	30	3	56	8	0.03	6	2.5	5	84	0	L	—	67
68	6	90	120	0.16	0.09	0.32	8	25	0	RS	0	23	13	0.03	20	20	3	20	3	0.04	3	5	d1	63	2	D	—	68
69	6	−110	110	0.16	0.08	0.32	0	8	13	R	0	20	0	0.04	12	15	1	8	5	0.03	5	−4	3	80	—	L	—	69
70	6	−35	112	0.16	0.08	0.32	0	6	15	R	0	25	0	0.05	40	40	14	34	12	0.03	5	−4	4	80	—	D	7.5	70
71	6	140	110	0.16	0.07	0.28	2	13	3	Rs	0	25	1	0.05	40	24	5	14	5	0.04	3.5	−3	2	65	—	L	—	71
72	7	140	85	0.17	0.06	0.36	0	11	0	rsR′	0	15	1	0.05	10	28	1	8	20	0.02	−1	2	2	90	1	L	8.2	72
73	7	100	130	0.12	0.08	0.28	0	7	4	rsR′	0	12	8	0.04	20	32	4	9	0	0.03	2	−4	2.2	90	—	L	9.4	73
74	7	60	110	0.14	0.08	0.30	0	22	8	RS	0	12	15	0.03	28	34	2	25	0	00.4	5	−1.7	3.5	50	—	L	18.7	74
75	7	60	110	0.18	0.07	0.33	0	12	8	Rs	0	17	3	0.03	30	28	8	40	5	0.04	9	−3	4	50	—	L	—	75
76	7	70	140	0.14	0.06	0.26	0	28	2	Rs	0	10	4	0.04	30	30	2	40	0	0.04	3	−1	2	68	0	D	—	76
77	7	88	120	0.14	0.08	0.28	0	19	3	R	0	11	0	0.05	45	60	3	28	4	0.03	6	1.5	3	88	1	L	—	77
78	7	130	140	0.14	0.08	0.30	0	11	7	R	0	20	0	0.05	40	20	3	24	6	0.04	4	−2	1.2	44	1	L	8.2	78
79	7	100	85	0.20	0.08	0.32	0	9	8	rsR′	0	24	4	0.06	30	24	8	17	17	0.04	−2	−2	−1.5	80	0	L	—	79
80	8	120	100	0.12	0.08	0.32	5	7	0	R	0	20	0	0.06	36	46	2	7	5	0.03	1.5	2.1	3	111	3	D	3.3	80
81	8	62	100	0.18	0.08	0.34	0	21	4	rSR′	0	13	10	0.06	20	30	6	30	6	0.03	2	−2.6	−1	80	0	L	7.9	81
82	8	−140	90	0.13	0.10	0.36	0	10	12	rsR′	0	36	4	0.04	12	25	2	12	13	0.04	6	−4	4	60	1	D	—	82
83	8	30	100	0.18	0.12	0.36	0	18	7	rsR′	0	33	6	0.04	40	54	7	40	8	0.04	5.5	−6	3.8	70	—	L	—	83

Individual ECG Measurements—Continued

				Lead 2				Lead aV$_F$			Lead V$_1$				Lead V$_5$			Lead V$_6$			T Wave						
Case	Age	Axis	Rate	P-R	QRS	Q-T	Q	R	S	Pattern	Q	R	S	In. Def.	R	S	Q	R	S	In. Def.	aV$_F$	V$_1$	V$_5$	Pul. Art. Sys. Pr.	Lung Grade	Status L or D	Pul. Flow Sq. M.	Case
84	8	115	100	0.10	0.06	0.32	0	15	0	RS	0	13	11	0.04	30	36	3	30	0	0.03	6	3	1.5	85	3	D	9.9	84
85	8	130	90	0.13	0.05	0.32	0	10	13	R	0	14	0	0.04	20	25	2	20	15	0.03	5.5	2	5	85	—	L	—	85
86	9	30	80	.013	0.11	.040	0	10	8	rSR′	0	25	13	0.07	17	10	1	52	4	0.04	5.5	−5	5	40	—	L	—	86
87	9	120	80	0.16	0.12	0.40	0	17	5	rsR′	0	30	1	0.05	24	26	2.5	20	20	0.03	3	−2.5	5	100	3	D	8.7	87
88	9	−175	100	0.12	0.08	0.30	0	10	12	R	0	20	0	0.04	30	50	0.5	10	11	0.02	4	3	3	74	3	D	—	88
89	9	−40	110	0.18	0.10	0.28	0	8	22	qrS	4	7	50	0.04	36	72	2	46	8	0.06	8.5	4	−6	105	3	D	21.2	89
90	9	85	90	0.16	0.08	0.32	0	17	8	rsR′	0	6	1	0.05	20	50	4	40	8	0.04	3	−2	2	71	0	L	8.1	90
91	10	−70	90	0.16	0.07	0.36	2	14	3	R	0	20	0	0.06	24	24	5	18	8	0.04	3	3	5	95	3	D	3.4	91
92	10	0	90	0.12	0.08	0.36	0	6	10	RS	0	20	20	0.04	50	34	2	9	0	0.05	3.5	−2.7	2.5	95	3	L	—	92
93	10	92	120	0.14	0.08	0.34	6	36	0	rsR′	0	22	5	0.05	30	10	1	32	8	0.04	−1	−2.5	2	121	3	D	14.0	93
94	12	40	90	0.14	0.06	0.36	0	18	11	R	0	10	0	0.05	25	26	4	28	0	0.03	3	−1	−2	75	—	L	.....	94
95	13	145	80	0.16	0.08	0.36	3	13	0	R	0	18	0	0.04	24	36	0.5	15	15	0.02	4.5	2	3	95	—	L	—	95
96	13	10	110	0.20	0.12	0.32	0	8	15	rsR′	0	22	1	0.08	20	16	6	20	6	0.05	4	−2.5	6	105	2	L	11.8	96
97	13	80	90	0.18	0.08	0.36	4	28	0	R	0	12	0	0.02	50	20	2	25	1	0.04	5	−1	4	80	—	L	—	97
98	14	140	100	0.18	0.10	0.32	0	7	3	R	0	15	0	0.08	25	20	2	20	8	0.04	3.5	−3.8	7	90	—	L	—	98
99	14	92	80	0.22	0.06	0.34	0	25	6	rS	0	3	13	0.02	20	60	4	39	3	0.04	6	−1	4	85	2	L	10.0	99
100	15	120	110	0.20	0.08	0.28	5	50	1	Rs	1	15	1	0.04	44	46	2	28	0	0.05	−2	−3	−3	73	3	D	11.8	100

Acute Ataxia of Childhood: A Summary of Fifteen Cases

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Ataxia is a symptom commonly encountered in children. From a therapeutic and prognostic standpoint, ataxia produced by posterior fossa tumors and spinocerebellar degeneration must be differentiated from that which is symptomatic of a more benign self-limited disease. Shanks [1] observed that a poor prognosis was usually associated with ataxia of insidious and chronic onset. On the other hand, spontaneous recovery usually occurred in children in whom ataxia had developed acutely. This condition has been referred to as "acute cerebellar ataxia." It is generally a benign disorder, subsiding in a few days or weeks. Adults are only rarely affected. The etiology is often undetermined, but in most cases it is thought to be a cerebellar encephalitis of infectious or toxic origin. The following is a summary of the clinical picture and a discussion of possible etiologies based on reports in the literature and our own observations of 15 cases.

Clinical Picture

The most characteristic clinical feature [2-6] is the abrupt onset of a grossly ataxic gait. This often occurs in a previously well child and sometimes during the convalescent phase of one of the childhood viral infections. The usual story is that the child awoke in the morning or from his afternoon nap and fell upon attempting to walk. It is then discovered that he walks with a staggering gait, falling frequently.

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The ataxia is the most striking and often the only abnormality observed. In some cases, intention tremors of the upper extremities are present. Occasionally nystagmus, dysarthria, hypotonia, and dysmetria are also demonstrated. At times there are signs of dysfunction in other parts of the nervous system, such as lethargy, cloudy sensorium, myoclonic movements, and cranial nerve palsies. Headache is rarely complained of, and there is usually no nuchal rigidity. Fever, nausea, and vomiting may be present. The spinal fluid is often normal but may contain a moderate excess of mononuclear cells and protein. Recovery occurs within one week to eight months, usually in one to three weeks.

Etiology

The syndrome of acute ataxia has been reported to occur in association with several of the viral diseases common in childhood. Underwood [7] stated that cerebellar symptoms are the most common central nervous system complications of varicella, and Galli [8] reported two cases of this type. Of 67 cases of rubeola encephalitis reported by Tyler,[9] there were cerebellar signs in 22 cases: in 3 cases, these were the only objective indications of central nervous system involvement. In eight of Griffith's [2] cases of acute cerebellar ataxia, measles preceded the development of ataxia. Ford [10] states that it is "not unusual to find during convalescence from measles, all the usual signs of cerebellar ataxia." Baker [11] mentions ataxia as one of the cerebral complications of rubeola, rubella, varicella, smallpox, and scarlet fever. Holub [12] reported a case of

acute ataxia with serologic evidence of mumps, without parotitis.

CASE 1.—A 10-year-old boy was admitted to the City of Memphis Hospitals on April 3, 1957. Two days prior to admission, he had awakened in the early morning with a frontal headache. Upon getting out of bed, he fell and was unable to walk without assistance. Four of his six siblings had had parotitis during the previous four weeks. The patient had never had parotitis or orchitis. On examination, he had a temperature of 102 F. There was no parotid swelling. He had a grossly ataxic gait and was unable to walk without assistance. Trunkal ataxia was present in the sitting position, and there was a mild terminal tremor of the upper extremities. There was no nystagmus, dysarthria, or dysmetria. The spinal fluid examination was normal. The complement-fixation titer for mumps was 1:64 on April 4, 1957. Unfortunately, a second specimen was not obtained.

A cerebellar form of poliomyelitis was suspected many years ago. Since the development of tissue culture and serologic methods of proving the diagnosis, several cases of acute ataxia due to this virus have been reported.[13,14]

CASE 2.—A 4-year-old boy was admitted to the City of Memphis Hospitals on August 2, 1957. On the day prior to admission, the patient awoke in the morning and fell while trying to walk to his mother's bed. It was then discovered that he could not walk without assistance. On the day of admission, he vomited several times and had three loose stools. He had never received poliomyelitis vaccine. He was afebrile and had no nuchal rigidity. Muscle strength was normal. He displayed a grossly ataxic gait and could not walk without aid. There was a trunkal ataxia in the sitting position. There was moderate dysmetria on finger pursuit and heel-to-knee tests. Nystagmus or tremor was not present. The spinal fluid contained 24 mononuclear cells with total protein of 23 mg. %. His symptoms continued for four weeks and then began to improve rapidly. He was discharged asymptomatic after six weeks of hospitalization. Neutralizing antibodies were present in the serum for poliomyelitis Type 3 in dilution of 1:4096 on August 4, 1957. The titer on September 4, 1957 was also 1:4096.

Influenza was mentioned as a possible cause of acute ataxia in five of Griffith's [2] cases and in three of the cases reported by Berglund et al.[14] Recently, Friedman and Cancellieri [15] described four cases of encephalitis associated with Asian influenza.

CASE 3.—A 4-year-old girl was admitted to LeBonheur Children's Hospital on October 29, 1957. Five days prior to admission, she had complained of sore throat. The following morning, while getting the child out of bed, the mother noticed that she could not stand alone and fell on attempting to walk. She became anorexic and vomited twice in the next three days. She had had no immunizations of any type. On admission, she was afebrile. Her gait was grossly ataxic, and unassisted walking was impossible. Violent intention tremor was present in all four extremities, and her speech was slurred. There was no nystagmus, muscle weakness, or other neurological abnormality. Examination of the spinal fluid revealed three cells and a total protein of 14 mg. %. On the second hospital day, her temperature rose to 103 F. On the fourth day, she became afebrile and began to improve rapidly. By the ninth day, she was asymptomatic. Blood specimens for virus studies were taken on October 30, 1957 and November 15, 1957. On the first specimen, a hemagglutination inhibition titer of less than 1:5 was reported for influenza Type A, Far East strain. On the second specimen, the titer was 1:10.

Acute ataxia has been reported in association with other infectious diseases. Hoyne [16] described a case with infectious mononucleosis. Ford [10] relates that incoordination of the cerebellar type has been associated with diphtheria in a few cases. Both Batten [3] and Griffith [2] described cases in association with typhoid.

More often the syndrome of acute ataxia occurs without an identifiable associated illness, and no etiologic agent can be found. Thus, in the cases described by Klingman and Hodges,[4] Goldwyn and Waldman,[5] and Cottom,[6] no cause was ascertained in any of the patients.

It is well known that certain exogenous toxins may cause cerebellar ataxia. The commonest ones are alcohol, barbiturates, and diphenylhydantoin. Bing and co-workers [17] reported that large doses of dichlorodiphenyl-trichloro-ethane (DDT) produced severe ataxia in dogs and concluded that DDT acts primarily on the cerebellum. Onifer and Whisnant [18] described a patient who developed cerebellar ataxia after exposure to the vapors of DDT and lindane. A history of exposure to insect sprays was obtained in several of our patients.

TABLE.—*Summary of Findings in Fifteen Cases of Acute Ataxia*

Case	Age, Yr.	Ataxia	Tremor	Dysarthria	Nystagmus	Fever	Nausea, Vomiting	Headache	Other Signs	CSF Abnormal	Viral	Titers	Duration, Days	Remarks
1	10	+	+	0	0	+	0	+	Lethargy	0	Mumps *	1:64	6	
2	4	+	+	0	0	0	+	0	Lethargy	Cells 24	Polio, Type 3	1:4096 1:4096	30	
3	4	+	+	+	0	+	+	0	0	0	Asian † influenza	>1:5 1:10	9	
4	2	+	0	0	0	0	0	0	Lethargy	0			2	Exposure to insect spray
5	7	+	0	0	0	0	+	0	Lethargy	0	Mumps	1:16 1:16	11	
6	5	+	0	0	0	0	+	0	0	0			2	Exposure to insect spray
7	4	+	+	+	0	+	+	0	Facial Palsy	Cells 131	Polio ‡ Type 3	1:128 1:128	30	
8	2	+	0	0	0	0	+	0	0	0			2	Exposure to insect spray
9	6	+	0	0	0	0	0	0	0	0	Polio, Type 3	1:1024 1:1024	2	
10	7	+	+	0	0	0	0	0	0	0			2	Exposure to insect spray
11	2	+	+	0	0	0	0	0	0	0	Polio, Type 1	1:256 1:256	21	
12	2½	+	0	0	0	+	0	0	0	0			7	
13	6	+	0	0	0	+	+	+	0	Cells 33			4	Varicella
14	12	+	0	0	0	+	+	+	0	0			2	Exposure to insect spray
15	7	+	0	0	+	+	0	+	0	Cells 44	Mumps	1:64 1:64	4	

* Complement-fixation.
† Hemagglutination inhibition.
‡ Neutralizing antibodies.

CASE 4.—A 2-year-old boy was admitted to the City of Memphis Hospitals on July 28, 1957. On the evening prior to admission, the patient had vomited his supper but otherwise had appeared to be well. On the morning of admission, he was noticed to stagger and fall on attempting to walk. On admission, he was afebrile. The only abnormalities noted were slight lethargy and grossly ataxic gait. There was no nystagmus, tremor, or dysmetria. Spinal fluid examination and serologic viral studies were normal. After 24 hours, his ataxia was greatly improved, and he was discharged asymptomatic on the fourth day. The mother stated that each night she sprayed the patient's room with an insect spray containing DDT. All windows and doors were closed, and the patient went to bed in the room about 10 minutes after the spraying.

Comment

The table is a summary of our observations in 15 cases. Most of the serologic data are inconclusive, since a four fold rise in titers was not demonstrated. However, the high titers for poliomyelitis neutralizing antibodies in Cases 2 and 9 suggests a recent infection with this agent. None of the patients had received poliomyelitis vaccine. Also, in Cases 4, 6, 8, 10, and 14, the significance of the exposure to insect spray is largely speculative. These observations, together with those reported by others, suggest that acute ataxia in childhood is a syndrome of diverse etiology. As Batten [3] first postulated, the disorder probably represents an encephalitis (or toxic encephalopathy) with a predominance of cerebellar symptoms. Most writers have emphasized the good prognosis, and all of our cases recovered completely and spontaneously.

Occasionally, symptoms caused by a cerebellar tumor may develop acutely, and this lesion must always be considered in children with acute ataxia. Headache and vomiting are more common with cerebellar tumors, but signs that should especially alert the clinician to the probability of this diagnosis are papilledema, tilting of the head, unilateral dysmetria, nystagmus which is more marked in one direction, sixth nerve palsy, high spinal fluid pressure, and x-ray findings of separation of the sutures, erosion of the clinoid processes and increased convolutional markings.

Summary

Ataxia of acute onset in children is thought to be symptomatic of various infections or toxic encephalopathies which affect the cerebellum predominantly. Careful examination and continued observation are mandatory for the exclusion of cerebellar tumors. Observations made in 15 cases suggest mumps, poliomyelitis, influenza, varicella, and intoxication from insecticides as possible etiologies. Acute ataxia has also been reported in association with rubeola, rubella, smallpox, scarlet fever, typhoid, infectious mononucleosis, diphtheria, and drug intoxication. The prognosis for complete recovery is good.

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Evaluation of Water-Soluble Hemisuccinate Esters of Hydrocortisone and Prednisolone

Plasma 17-Hydroxycorticosteroid Concentrations Following Intravenous Administration

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The adrenal steroids have assumed a role of major importance in clinical therapy during the past few years. Although clinical application of these compounds has been rapid and extensive, therapy of this type is not without complications and side-effects. As a result, a great deal of research emphasis has been placed upon attempts to synthesize new steroids with enhanced therapeutic effectiveness and with as few as possible deleterious or undesirable properties.

The first major advance in this direction resulted when the Δ^1-steroids, prednisone and prednisolone were synthesized.[1-4] These compounds are related structurally to cortisone and hydrocortisone, respectively, and differ from the parent steroids by having a double bond in the C-1 position. These Δ^1-steroids now have been given extensive trial and have been found to have wide clinical applicability. It has been postulated that the enhanced effectiveness of these compounds is due, in part, to delayed degradation in the circulating plasma, as compared with their parent steroids.[5]

In emergency situations intravenous steroid therapy frequently may be indicated. Cortisone, hydrocortisone, and their Δ^1-derivatives have been available for intravenous administration but only in the form of alcoholic solutions. For safety, these preparations must be diluted severalfold and administered by slow intravenous infusion. Obviously, this imposes serious limitations on their clinical usefulness.

It would be desirable, especially for use with pediatric patients, to have available for intravenous steroid therapy a preparation which could be administered as a single injection of small volume. Such preparations have been made available in the form of the steroid C-21 hemisuccinate esters of cortisone, hydrocortisone, prednisone, and prednisolone. If these esters prove to be as effective clinically as the alcoholic solutions of the steroids, the major disadvantages of intravenous steroid therapy will have been eliminated.

The purpose of the present study is to compare the steroid hemisuccinates with the corresponding free steroids in regard to their effects on circulating concentrations of free (nonesterfied) 17-hydroxycorticosteroids (17-OHCS).

Materials and Methods

Volunteer normal young adults were the subjects for all studies reported. In one group, each of nine subjects was given a rapid intravenous injection of

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TABLE 1.—*Plasma 17-OHCS Concentration After Intravenous Administration of Steroids to Normal Human Subjects* *

Steroid Preparation		Time					
		30	60	90	120	180	240
F alcohol, 1 mg/kg.							
	1	83	87	42	59	38	
	2	89	73	45	47	37	
	3	74	62	54	37	21	
	4	134	88	74	61	41	
	5	119	77	70	--	35	
	6	98	83	65	59	43	
	7	114	90	69	40	28	
	8	97	80	63	60	--	
	9	104	85	64	40	30	
		—	—	—	—	—	
	Mean	101	81	60	50	34	
F hemisuccinate, 1 mg/kg.							
	1	58	55	--	41	--	24
	2	64	63	--	35	--	18
	3	42	37	--	27	--	17
	4	55	48	--	32	--	14
	5	63	53	--	41	--	23
	6	61	45	--	32	--	16
	7	65	68	--	38	--	12
	8	61	47	--	22	--	11
	9	73	56	--	40	--	16
		—	—	—	—	—	—
	Mean	60	53	--	34	--	17
Δ^1-F alcohol, 0.5 mg/kg.							
	1	--	52	--	31	33	22
	2	--	45	--	--	33	26
	3	--	55	--	43	27	24
	4	--	40	--	33	30	21
	5	--	43	--	31	25	22
	6	--	60	--	35	31	32
	7	--	56	--	43	41	27
	8	--	49	--	35	25	27
		—	—	—	—	—	—
	Mean	--	50	--	36	31	25
Δ^1-F hemisuccinate, 1 mg/kg.							
	1	56	35	34	32	17	
	2	78	48	49	36	32	
	3	64	--	43	47	36	
	4	60	55	44	38	33	
	5	55	--	49	42	40	
	6	47	52	40	41	33	
	7	52	48	44	38	26	
	8	66	53	49	37	24	
		—	—	—	—	—	
	Mean	60	48	44	39	30	

* Concentration given in μg. %.

hydrocortisone-21-hemisuccinate (F-hemisuccinate *) on the basis of 1 mg. per kilogram of hydrocortisone equivalent. Blood samples were obtained at 30, 60, 120, 240, and, in 2 subjects, 360 minutes after injection. In a second group, of eight subjects, each was given a rapid intravenous injection of Δ^1-hydrocortisone-21-hemisuccinate (Δ^1-F-hemisuccinate †) in a dose of 1 mg. per kilogram, Δ^1-F equivalent. Blood samples in this group were obtained at 30, 60, 90, 120, and 180 minutes after injection. Plasma was separated from the specimens immediately and kept frozen until used for determination of 17-OHCS concentrations by the method of Nelson and Samuels.[6,7]

* Solu-Cortef, supplied by Dr. C. J. O'Donovan, The Upjohn Company, Kalamazoo, Mich.

† Delta Cortef Hemisuccinate, supplied by Dr. C. J. O'Donovan, The Upjohn Company, Kalamazoo, Mich.

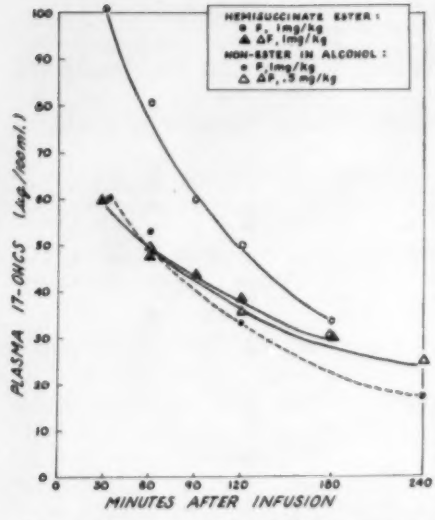

Fig. 1.—Mean circulating 17-OHCS concentrations following intravenous administration of steroid as the free alcohol or hemisuccinate ester.

In each case the resulting data were plotted semilogarithmically and the regression line of best fit was determined by the method of least squares; the half-life of the administered steroid was calculated from the slope of that regression line.

In a previous study,[6] data were presented for 17-OHCS blood levels and steroid half-life after the intravenous administration of the free (non-ester) form of hydrocortisone and Δ^1-hydrocortisone. These data obtained are used again here for comparison with the new data obtained with use of the hemisuccinate esters.

Results

The individual free 17-OHCS concentrations at various times after intravenous administration of hydrocortisone (F), Δ^1-hydrocortisone (Δ^1-F), and their respective hemisuccinate esters are shown in Table 1. At the bottom of each group, the mean values are listed for each time period. These mean values in turn are graphed in Figure 1. As shown in the Figure, at 30 and 60 minutes after the administration of 1 mg. per kilogram of hydrocortisone the mean 17-OHCS concentration was considerably higher than the corresponding 17-OHCS value after 1 mg. per kilogram of hydrocortisone hemisuccinate or Δ^1-hydrocortisone hemisuccinate. This difference was somewhat less at longer time intervals after administration of the drugs. Free Δ^1-F, given in a dose of 0.5 mg. per kilogram, resulted in 17-OHCS values which were about the same as those produced by the hemisuccinate esters of F and Δ^1-F in a dose of 1 mg. per kilogram. Thus, within the first three or four hours after administration, the ester forms did not give blood levels of hydrolyzed steroid comparable to those produced by the free steroids.

Data concerning the 17-OHCS half-life, for both individual subjects and group means, are shown in Table 2 for the intravenously administered steroids being studied. As reported previously,[5] the mean 17-OHCS half-life value after the administration of Δ^1-hydrocortisone was significantly longer than the value after administration of hydrocortisone. Similarly, the mean 17-OHCS half-life value after the administration of Δ^1-hydrocortisone hemisuccinate was significantly longer than the value after administration of hydrocortisone hemisuccinate. Thus, the Δ^1 structure delayed steroid metabolism considerably.

TABLE 2.—*17-OHCS Half-Life Values After Intravenous Administration of Steroids to Normal Human Subjects*

Hydrocortisone				Δ^1-Hydrocortisone			
Alcohol, * 1 Mg/Kg.		Hemisuccinate 1 Mg/Kg.		Alcohol * 0.5 Mg/Kg.		Hemisuccinate † 1 Mg/Kg.	
Subject	Half-Life	Subject	Half-Life	Subject	Half-Life	Subject	Half-Life
1	128	1	155	1	189	1	97
2	114	2	124	2	217	2	131
3	81	3	158	3	141	3	201
4	94	4	102	4	205	4	158
5	90	5	148	5	185	5	301
6	126	6	108	6	232	6	274
7	70	7	128	7	171	7	177
8	124	8	83	8	197	8	100
9	79	9	95	--	--	--	--
Mean	101		122		193		160
S. E. M.	7.4		9.1		9.9		26.8

* Data from previous report.[6]

† The data following administration of Δ^1-F hemisuccinate to subject 9 (presumably normal) were not included in the Table because they were so aberrant: the 17-OHCS half-life obtained was 450 minutes.

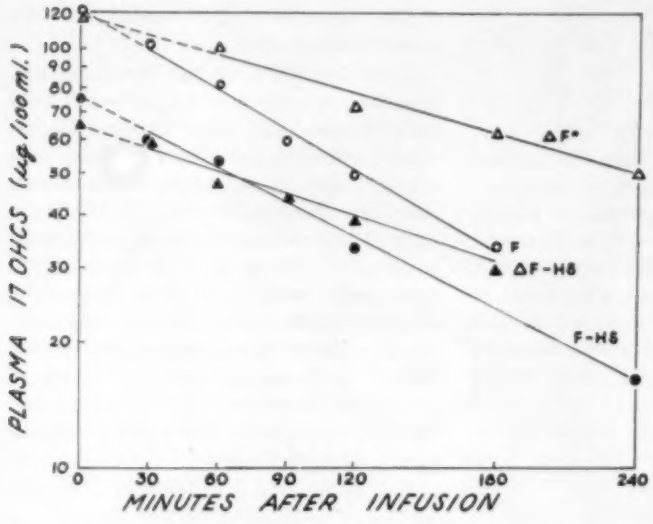

Fig. 2.—Logarithmic regression of circulating 17-OHCS concentrations following intravenous administration of steroid as the free alcohol or hemisuccinate ester. HS indicates hemisuccinate ester; *, mean 17-OHCS values for Δ^1-F were doubled to correct for the difference in dose.

The half-life for 17-OHCS after administration of the hemisuccinate esters and their parent steroids did not differ significantly: the mean 17-OHCS half-life for F-hemisuccinate was increased suggestively over that for F (122 vs. 100 minutes), but that for Δ^1-F hemisuccinate was slightly shorter than that for Δ^1-F (180 vs. 193 minutes).

In Figure 2, the calculated regression line, logarithmically representing the mean blood level of free steriod plotted against time, is shown for each steroid administered. This illustrates graphically the relative magnitude of the difference seen. Here the mean 17-OHCS values for Δ^1-F were doubled to correct for the difference in dose. The two major points illustrated by these curves are as follows: 1. Lower plasma steroid values occurred following administration of each hemisuccinate than following administration of the corresponding free steriod. 2. The rate of disappearance depended upon the presence or absence of the Δ^1 unsaturation but not upon the presence or absence of the hemisuccinate ester in the steriod administered.

Comment

The availability for intravenous use of lyophilized water-soluble forms of steroids, such as the hemisuccinate esters tested in this study, has significant clinical value. The advantage of mixing in small volumes and administering by rapid intravenous injection rather than using the large volume dilutions necessary with the alcoholic steroid solutions is considerable. The present study compares the concentrations of steriod in the free form obtained after administration of the steroid as the hemisuccinate ester and as the alcoholic (nonester) preparation.

A previous study [5] has shown that prednisolone is measured as a 17-hydroxycorticosteroid by the Nelson and Samuels method, which was employed here.[6,7] Steroid hemisuccinates, on the other hand, are not measured by this method until de-esterification, i. e., conversion to the free form, has taken place.[8] Similarly, the acetate and cyclopentylpropionate esters of hydrocortisone are not measured by this technique.[9]

The use of the regression lines of best fit for comparison of data obtained in studies of intravenously administered steroids is valid in studies employing free steroids, since these steroids disappear from the circulation in a manner consistent with a first order reaction. However, in the case of the steroid hemisuccinate esters a two-phase reaction is involved. In this case, the com-

pound introduced is not measured by the method used until hydrolysis of the esters occurs, releasing free steroid into the circulation. This free steroid then disappears from the circulation in the usual manner.

As observed, plasma 17-OHCS values for the hemisuccinate derivatives are considerably lower than those for steroids in alcohol, indicating that when equivalent doses are administered less free circulating 17-OHCS results from the steroid esters. In terms of total steroid given, one might expect that continued release of free steroid from the ester by hydrolysis would ultimately supply an equal dose of free steroid over a more prolonged period. Collins [8] implies this in his conclusions from his studies on dogs. Evaluation of his half-life data, however, reveals differences that are not significant statistically. Our results also show insignificant differences. Assuming from this that, in fact, more prolonged levels do not occur, one can postulate that significant alterations in the 17,21-dihydroxy-20-keto configuration may take place while the steroid is still in ester combination. Jakoby and Thompkins [10] studied the metabolism of pregnan-21-ol-3,20-dione 21-hemisuccinate in rat-liver preparations. They showed that the main metabolic pathway is through ester hydrolysis, followed by C-3 carbonyl reduction, but that some carbonyl reduction takes place before completion of ester hydrolysis. It is conceivable that a similar coincidence of enzymatic alterations could take place in the steroid hemisuccinate esters studied here. This may provide only a partial explanation, however. Another consideration is that a significant portion of the ester form may remain as such and that most of the hydrolysis which does take place may occur rather promptly. It is possible also that the hemisuccinate esters may penetrate tissues or be excreted more rapidly, leaving less of the esterified compound remaining in the blood to be hydrolyzed to the free steroid. Additionally, the presence of a double bond at C-1 in Δ^1-F may in some way interfere with the ester hydrolysis at C-21. The data of Collins [8] might suggest this, but the data reported here do not.

From the results of this study and that of Collins, it appears that there are at least three factors that relate to the expected clinical effectiveness of the hemisuccinate steroid esters: 1. When the hemisuccinate esters are administered, free 17-OHCS are released into the circulation in considerable amounts. 2. The levels thus produced are significantly lower than those effected by equivalent doses of the free steroids in alcoholic solution (approximately 30% to 50% lower). 3. Administration of the hemisuccinate ester does not seem to cause a significant prolongation of elevated circulation plasma 17-OHCS levels.

It is apparent that water-soluble steroids for rapid intravenous injection would be useful in certain emergency situations. Therapeutic levels of free 17-OHCS could be expected with assurance in most situations, but the dosage used would have to be increased to give blood levels equivalent to those obtained with the free steroids. The data obtained from one apparently normal subject (Subject 9, footnote to Table 2) illustrate this point. Administration of Δ^1-F hemisuccinate (1 mg. per kilogram) resulted in low plasma 17-OHCS values and a half-life of 450 minutes. This may have been the result of a relative inability on the part of this subject to de-esterify the steroid given, although it is possible that this may have resulted from an inapparent extravasation of the injected fluid.

Further clinical trials of steroid hemisuccinate esters are indicated to evaluate their clinical effectiveness better, particularly regarding variations in individual response; such variations may be considerable even in normal subjects, as is suggested by the data presented concerning subjects given Δ^1-F-hemisuccinate. Especially might this be true in acutely ill patients whose ability to de-esterify the steroids might be impaired. If this were the case, little free steroid would be released into the circulation.

Summary

This study is concerned with the effects on plasma 17-hydroxycorticosteroid (17-OHCS) concentrations of hydrocortisone and Δ^1-hydrocortisone in ester combination with hemisuccinate when administered intravenously to normal human subjects. The plasma 17-OHCS concentrations thus produced were lower than those produced by equivalent doses of free steroids in alcoholic solution. The 17-OHCS half-life values after administration of the hemisuccinate esters were essentially the same as those after administration of the free steroids. The lower 17-OHCS levels attained after administration of the hemisuccinate may be due in part to some degradation of the 17,21-dihydroxy-20-keto structure before deesterification is complete. The data suggest that the steroid hemisuccinate esters should be effective clinically but that the dose required to produce equivalent blood levels of free steroids would be somewhat higher for the hemisuccinate esters of steroids than for the parent compounds. Further studies of hemisuccinate steroid esters are warranted.

Stanford University Hospital, San Francisco (Dr. Done).

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Congenital Malformation of the Cardiac Conduction System

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Congenital conduction defects of the heart have heretofore been grouped heterogenously in the literature under the broad term "congenital heart block." This title is somewhat inappropriate, since it connotes a basic physiologic rather than an anatomic disorder. Because the atrioventricular block is actually the result of an underlying anatomic defect, it would probably be preferable to classify this condition anatomically as with other congenital heart lesions, rather than physiologically. When malformations involve the cardiac conduction system, gross anatomic heart defects, according to published data, are extremely common.[1-15] However, in rare instances the pathology has been reported to be only microscopic.[15-20] Since modern diagnostic methods now enable us to establish ante mortem the precise nature of anomalies of this type, we can separate with a reasonable degree of accuracy those patients with purely microscopic lesions from those in whom there are complicating gross anatomic defects of the heart. The importance of this differentiation becomes apparent when one considers that the management, as well as the prognosis, differs greatly in these two groups.

The purpose of this paper is threefold: first, to report a case of congenital interruption of the cardiac conduction system unassociated with other defects and diagnosed during life; second, to establish this condition as a separate clinical and pathologic entity,* and finally, to suggest a change from the present nomenclature of "congenital heart block" to the more appropriate term of "congenital malformation of the cardiac conduction system, with or without associated gross cardiac defects."

Report of Case

This 5-year-old girl was suspected antenatally of having a complete atrioventricular block, the presence of which was confirmed by an electrocardiogram shortly after birth. A detailed description of these events has been presented elsewhere.[21] The child has since remained in a state of excellent health. However, persistence of a Grade 3 systolic murmur maximal at the fourth left intercostal space, associated with roentgenographic evidence of cardiac enlargement, suggested the presence of an interventricular septal defect. The case was recently discussed with Dr. Paul Adams, Jr.,† who stated that on the basis of his experience he believes a number of patients with this clinical picture have no gross anatomic lesions of the heart. It was therefore decided that a comprehensive investigation of this patient be undertaken to determine the exact nature of her abnormality. She was accordingly admitted to the Medical Center of the University of California at Los Angeles, where this study was performed. The results were as follows.

Teleroentgenograms.—Roentgenographic examination disclosed minimal but definite widening of the left border of the heart. It could not be determined from a study of the oblique views which ventricular chamber was affected. The pulmonary segment was prominent, but the lung fields were normally vascularized (Fig. 1).

Electrocardiogram.—The electrocardiogram revealed a complete atrioventricular dissociation, the auricular rate being 110 per minute and the ventricular 60 per minute. There was no evidence of specific chamber hypertrophy (Fig. 2).

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Dr. Burton W. Fink assisted in the interpretation of the phonocardiogram.

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* This concept was first suggested by Wallgren et al.[17] and more recently by Mathieu et al.[20]

† Assistant Professor of Pediatrics (Cardiology), University of Minnesota Medical School.

Fig. 1.—Teleroentgenogram taken with the patient in the posterior-anterior position. There is prominence of the pulmonary segment and slight widening of the left border of the heart.

Phonocardiogram.—Phonocardiographic tracings confirmed the presence of a loud cardiac murmur. It occupied all of systole and was of maximal intensity in the second interspace to the left of the sternum (Fig. 3).

Cardiac Catheterization.—Right heart catheterization was performed with a No. 7 Goodale-Lubin single-lumen triple-orifice cardiac catheter. The patient was maintained in a state of basal anesthesia by the rectal administration of 10% thiamylal (Surital). A P23D Statham strain gauge was used, and the pressure tracings were recorded on a six-channel direct-writing Offner recorder.

Analysis of the data disclosed no evidence of shunting of blood between the two systems. The pressures, however, were elevated throughout the entire right side of the heart, as well as in the left atrium and the left superior pulmonary vein. The latter two structures had been entered by way of a foramen ovale which was believed to be functionally closed. The catheterization data are presented in the Table.

Selective Angiocardiography.—Biplane angiocardiograms were made at six frames per second following the automatic injection of 50% sodium diprotrizoate (Miokon Sodium) into the right ventricle. This study confirmed the impression at catheterization that no septal defect was present. The valvular structures and ostia also appeared to be normal. However, both the aortic and the pulmonic trunk were moderately dilated (Fig. 4, *A* and *B*).

Comment

A study of the literature relating to congenital heart block reveals that there is almost always an associated gross anatomic anomaly of the heart, usually an interventricular septal defect.[1,2,5-9,11-15,22] More recent evidence suggests that corrected transposition of the great vessels also may frequently be associated with atrioventricular heart block.[23] There appears, however, to be a small group of patients in whom the heart is normally formed and the dissociation is a

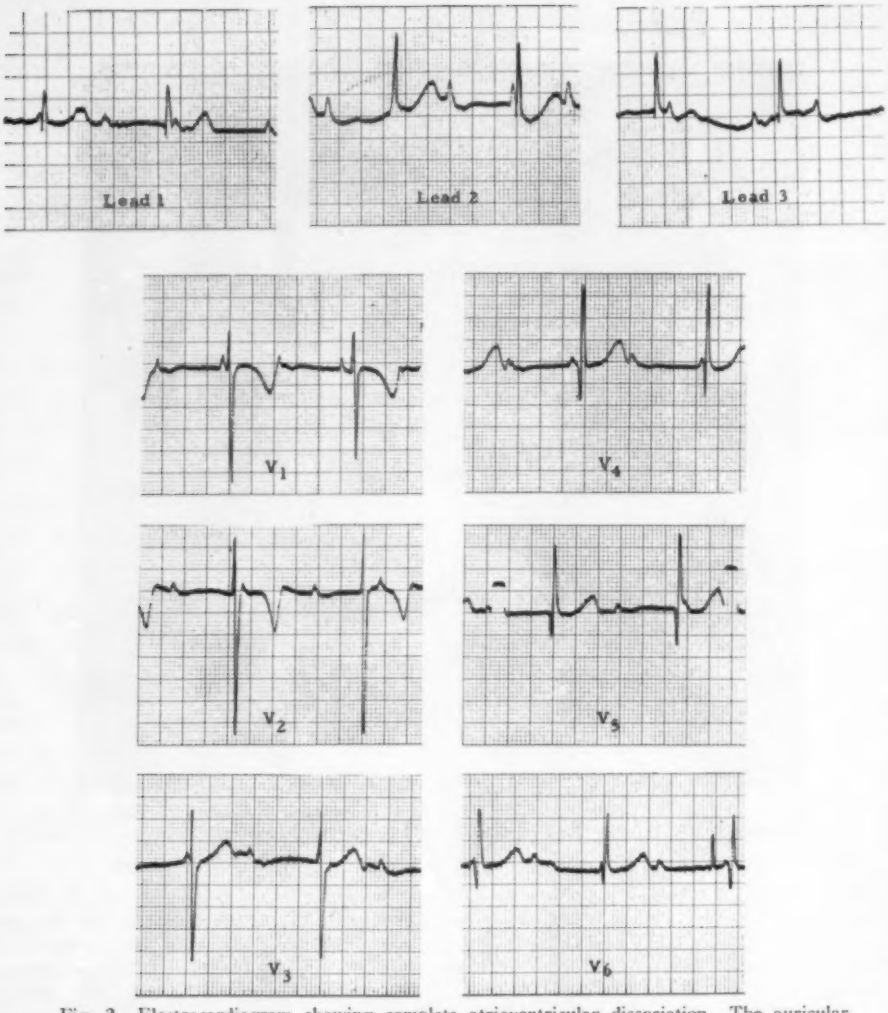


Fig. 2.—Electrocardiogram showing complete atrioventricular dissociation. The auricular rate is 110/min. and the ventricular, 60/min. There is no definite evidence of chamber hypertrophy.

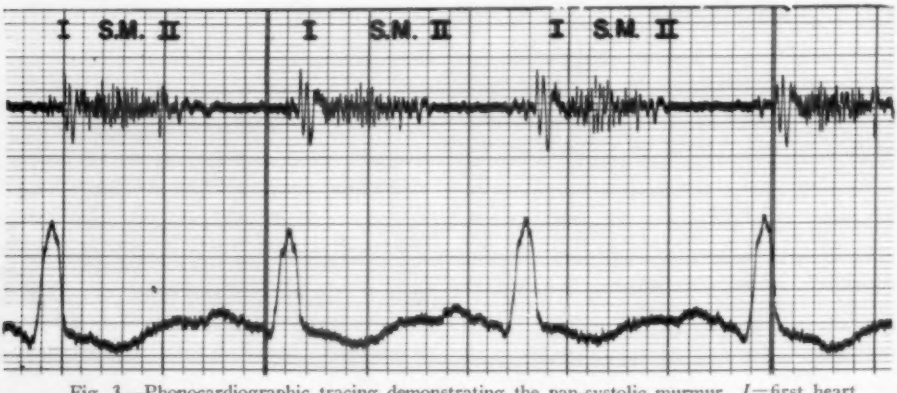


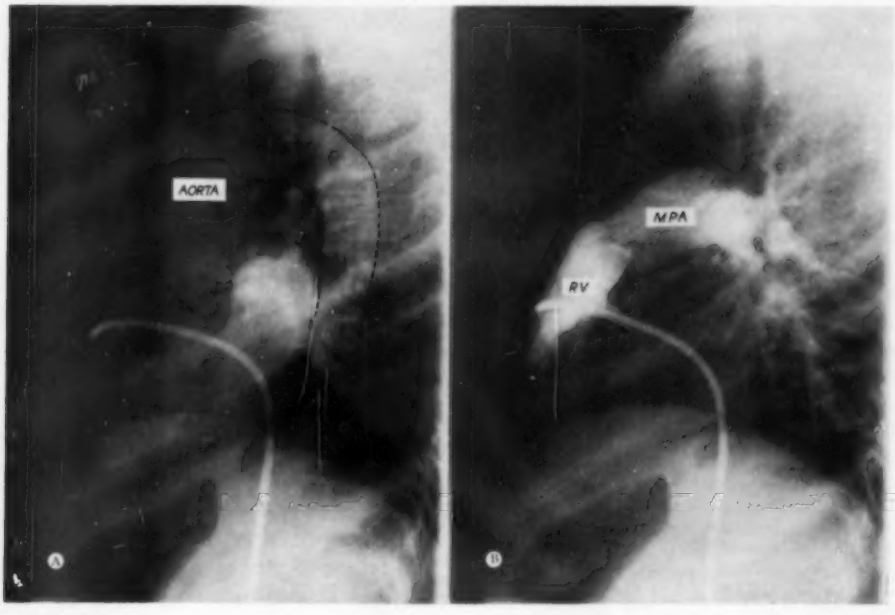
Fig. 3.—Phonocardiographic tracing demonstrating the pan-systolic murmur. *I*=first heart sound. *II*=second heart sound. *S. M.*=systolic murmur.

Cardiac Catheterization Results Showing Generalized Increased Intracardiac Pressures and No Evidence of Shunt

	Superior Vena Cava	Inferior Vena Cava	Right Atrium	Right Ventricle	Pulmonary Artery	Left Atrium	Pulmonary Vein
Pressure, mm. Hg.	12/7	11/6	11/6	40/9	31/9	20/10	22/11
Average oxygen saturation, %	67	76	69	70	70	92	92

result of an isolated microscopic lesion of the conducting system. This has been confirmed by postmortem study in three patients.[17-19] An additional three patients have been studied clinically and found to have no gross abnormality at cardiac catheterization.[15,16,20] Thus, a total of six patients with isolated interruption of the cardiac conduction system has been recorded in the literature. Undoubtedly, there are many more unreported cases as evidenced by the relatively large number of patients studied by Adams.[24] He performed right heart catheterization in nine patients with congenital complete atrioventricular dissociation, and in none did he find any evidence of intracardiac defects. Failure to confirm by right heart catheterization and angiocardiography the previously published impression of an interventricular septal defect in our patient suggests that the diagnosis may be in error in other cases which have been supposedly documented in the literature. Further support of this is offered by Campbell and Thorne, who recently published long-term observations on seven patients with congenital heart block.[25] Whereas originally most of these patients were reported probably to have interventricular septal defects.[1,20] recent reevaluation revealed no good evidence of this or any other congenital defect.[25] In fact, in five of the patients the murmur was believed to be purely functional or cardiorespiratory in origin. It is of in-

Fig. 4.—Angiocardiogram showing dilatation of the aorta (A) and of the main pulmonary artery (B). *MPA*=main pulmonary artery. *RV*=right ventricle.



terest that to date the presence of gross cardiac malformations in association with congenital heart block has been confirmed at autopsy in only 17 cases.[15]

Congenital malformation of the cardiac conduction system occurring as an isolated lesion is extremely difficult, if not impossible, to diagnose during life without the aid of cardiac catheterization and/or angiocardiographic studies. The results of these studies in our patient proved to be most interesting. Although normal intracardiac pressures were recorded at catheterization in the three patients reported in the literature,[15,16,20] elevated pressures apparently do occur in some subjects, as evidenced by our findings and those of Adams.[24] This is not surprising, since the cardiac output is usually unaltered, and, therefore, the stroke volume must be elevated.‡ Moreover, when atrial systole occurs while the atrioventricular valves are closed, the atrial pressures increase.[27] These physiologic alterations can produce a clinical picture which is indistinguishable from that of an interventricular septal defect. The increased stroke volume and the elevated intracardiac pressures may eventually produce generalized cardiac enlargement, a pathologic finding which has been observed at autopsy in two such patients.[17,19] Relative valvular incompetence, dilatation of the arterial trunks, or the increased stroke volume in itself may produce a loud systolic murmur.

The importance of recognizing the two varieties of this disorder should not be minimized, since the management and prognosis differ greatly. Patients with the isolated type do not require definitive treatment. Their prognosis is probably very good in most instances, although the long-range effects of the physiologic alterations within the heart are not yet completely known. In contradistinction to these patients are those in whom the conduction defect is complicated by a grossly malformed heart. In these, operative intervention is often necessary, and the ultimate prognosis depends upon the associated anomaly. Events of recent years have made possible the recognition during life of these two groups of patients.

‡ In our patient the cardiac output was within the range of normal, being 3.3 liters per minute. Since her ventricular rate was only 60/min., the stroke volume was 55 cc.

Summary

Congenital malformations of the cardiac conduction system have until now been obscured in the literature under the general term "congenital heart block." Actually, two varieties of this disorder may be identified, one occurring in an otherwise normally formed heart and the other occurring in association with gross anatomic cardiac defects. Congenital heart block is common to both.

Evidence is presented which indicates that the true incidence of the isolated variety is probably greater than the number of published cases would indicate. The physiologic alterations are such that the clinical picture of an interventricular septal defect can be closely simulated. No treatment is required for this condition, and the prognosis is probably very good.

On the other hand, when cardiac conduction defects are complicated by gross anatomic cardiac abnormalities, the prognosis is variable, depending upon the associated anomaly. Surgical intervention is indicated in selected cases. Modern methods of diagnosis now make differentiation of these two conditions possible during life.

The case of a 5-year-old girl with complete atrioventricular dissociation since birth is presented. A diagnosis of malformation of the cardiac conduction pathways unassociated with other anomalies was established during life by right heart catheterization and selective angiocardiography.

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Addendum

Since this paper was submitted for publication, a report on 27 children with congenital complete atrioventricular block has appeared in the literature (Paul, M. H.;

Rudolph, A. M., and Nadas, A. S.: Congenital Complete Atrioventricular Block: Problems of Clinical Assessment, *Circulation* 18:183-190 (Aug.) 1958). Of 12 patients in this group who underwent right heart catheterization, only 4 showed evidence of intracardiac shunts.

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Virilizing Adrenal Tumors in Children

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Adrenal tumors in children under 10 years of age are relatively rare. In 1951 one of us (R. B. G.) placed on record a case of a virilizing adrenal tumor in a 3-year-old girl [1] and in reviewing the literature found 76 previously reported cases. From the time of that report until 1957, there have been approximately 30 additional cases.[2-26] In the interim, primarily as a result of an increased understanding of adrenal physiology, there has been considerable improvement in the techniques for the diagnosis of adrenocortical tumors.

As early as 1950, Wilkins [27,28] reported that the administration of cortisone suppressed the excretion of androgens in congenital adrenal hyperplasia, and he suggested the use of cortisone in the treatment of this condition.[29] The suppression of 17-ketosteroid excretion by cortisone was proposed as a test to aid in differentiating between adrenocortical tumor and hyperplasia.[30]

The findings of Wilkins and his associates led to studies of the metabolic dysfunction of the adrenal cortex by others, including Jailer,[31-34] Kelly,[35] Bartter,[36] Dorfman,[37] Eberlein,[38,39] and Bongiovanni.[24,40] These workers demonstrated that there was a fault in the synthesis of 17-hydroxycorticosterone (Compound F) which resulted in an increased production of corticotropins by the pituitary. Increased output of corticotropin (ACTH) in these patients was demonstrated as the immediate factor in the excessive production of androgens by the adrenal cortex. Furthermore, Bongiovanni [40] demonstrated that in many patients with congenital adrenal hyperplasia there was an

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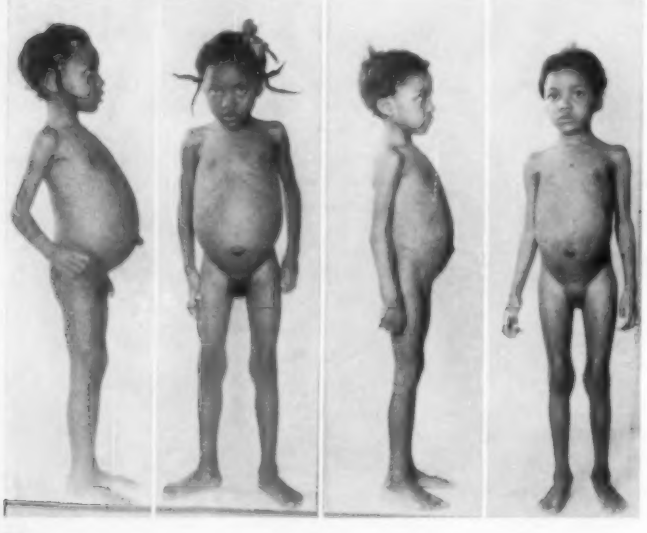


Fig. 1 (Case 1).—Negro girl aged 3½ years. Photographs taken before and after surgery.

Fig. 2 (Case 1).—Note enlarged clitoris, normal vaginal introitus.

excessive production of the steroid metabolite, pregnanetriol. With the development of a simplified method for the determination of pregnanetriol, Bongiovanni [41] suggested the employment of this assay as an aid in the differentiation between congenital adrenal hyperplasia and tumor.

Two cases are presented here to contrast criteria needed for the diagnosis of adrenogenital syndrome caused by tumor. One of them was reported in 1951 and differs from the second case presented in that the diagnosis of the latter case depended upon an understanding of all the more recently developed facts concerning adrenal physiology. It is the purpose of this paper to demonstrate how these diagnostic techniques were employed in arriving at the proper diagnosis.

Report of Cases

CASE 1 (review of previously reported case).—This 3½-year-old Negro girl (Fig. 1) was first seen by us in 1951.[3] She had a protuberant abdomen which had been increasing in size for the previous six months. Axillary and pubic hair and a markedly hypertrophied clitoris were present. The vaginal introitus was normal in appearance (Fig. 2). A large abdominal tumor was palpable. X-ray studies showed the bone age to be 10+ years. Urinary steroid studies (Table 1) revealed grossly elevated urinary 17-ketosteroids and an elevated pregnanediol complex. The Allen color test for dehydroepiandrosterone was strongly positive. Corticosteroid output was normal. Two exploratory laparotomies were performed, and two large tumors were removed. Both tumors were demonstrated to have arisen from the left adrenal

TABLE 1.—*Urinary Hormonal Assays* *

Date	17-Ketosteroids †	Pregnanediol	Allen Test †	Corticosteroids	Creatinine	Creatine
1-14-51	228.7	19.6	Pos.	0.65	202	39
1-15-51	102.3	18.0	----	0.27	148	50
1-16-51	Excision of central tumor					
1-21-51	324.0	18.4	----	0.72	270	14
1-23-51	190.6	23.5	----	0.13	107	78
1-23-51	257.0	31.1	----	0.07	232	0
1-24-51	132.2	42.6	----	0.10	260	220
1-25-51	115.0	--	----	0.06	--	--
1-26-51	130.0	--	----	0	226	185
1-27-51	318.6	--	----	0.16	480	180
1-28-51	289.8	--	----	0.08	240	82
1-29-51	222.7	--	----	0.18	224	26
2- 1-51	Excision of left adrenal tumor					
2- 8-51	2.8	--	Neg.	0.23	207	0
2- 9-51	1.4	--	Neg.	0.56	80	0
5-15-51	194.4	--	----			
5-16-51	248.0	--	----	0.32	282	141
5-21-51	700.0	--	Pos.	0.23	328	296
6-18-51	521.0	--	----	Recurrence with metastases		

*Data expressed in milligrams per 24 hours.

† Note return to normal of urinary 17-ketosteroids and Allen test after surgery and return to high 17-ketosteroid values and positive Allen test with recurrence of metastases.

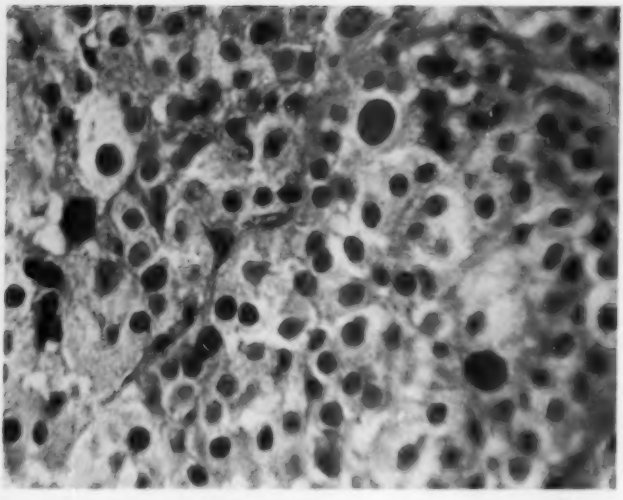


Fig. 3 (Case 1).—Photomicrography of histologic section of adrenal tumor showing marked cellular pleomorphism and hyperchromatic nuclei.

gland. There were extensive areas of necrosis throughout the neoplasm (Fig. 3).

After the operations the patient progressed well for approximately three months. The 17-ketosteroid excretion returned to normal, and the Allen test became negative. Soon thereafter, however, elevated 17-ketosteroid values, accompanied again by a positive Allen test, indicated a recurrence of the tumor. Pulmonary metastases were demonstrable on x-ray. The patient followed a downhill course and died (Table 1).

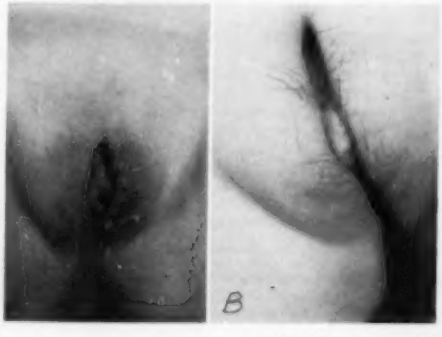
Case 2.—A 2-year-old Oriental girl was first admitted on July 23, 1957. The primary complaints of long black silky hair in the axillary region, pubic hair, and enlargement of the clitoris (Fig. 4) were first noticed about two months prior to her admission to the hospital. Examination revealed a child somewhat overdeveloped for her age (Fig. 5). The height was 95 cm. (37½ in.); weight 17 kg. (39½ lb. 9½ oz.). The extremities were very muscular. The urethral opening was of the hypospadic type. Further examination revealed a normal cardiovascular apparatus. Her blood pressure was 90/60 mm. Hg. Fundoscopy was negative. X-ray studies revealed that the sella turcica was within normal limits and the bone age was 4 years (Fig. 6). Intravenous pyelogram did not reveal any renal displacement. The buccal smear revealed a positive (female) sex chromatin pattern.

The impression on admission was either congenital adrenal hyperplasia or adrenal tumor. Urinary steroid determinations (Table 2) were suggestive of adrenal tumor. However, in the absence of other clinical findings to substantiate this diagnosis, the patient was placed on suppressive doses of hydrocortisone. Urinary steroid determinations performed on follow-up visits were still indicative of adrenal tumor (Table 2).

The patient was readmitted for a perirenal insufflation, and the results were inconclusive. In the light of repeated laboratory evidence suggesting adrenal tumor, surgical exploration of the left adrenal was decided upon. Exploration was performed by means of a left thoracoabdominal incision. The left adrenal gland appeared somewhat atrophic; part of the gland was removed for study. Palpation of the right adrenal gland was done at this time, and a small mass was felt. The uterus and adnexa were inspected and were found to be normal for a child of her age. The pathologic examination of the biopsy specimen of the left adrenal gland showed normal adrenal tissue.

A second operation was performed two weeks later, with use of a right thoracoabdominal ap-

Fig. 4 (Case 2).—Note enlargement of the clitoris and presence of pubic hair. *A*, before operation. *B*, after operation.



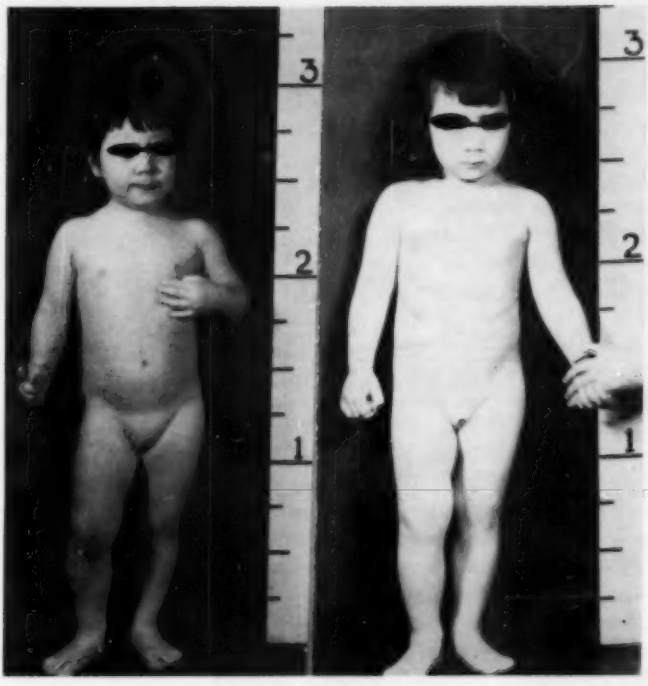


Fig. 5 (Case 2).—Before and nine months after operation.

proach. A firm well-encapsulated tumor of the right adrenal gland, 3 cm. in diameter, was found. The entire gland was removed. Prior to, during, and after the operation the patient was maintained on supportive doses of cortisone acetate and corticotropin. Water and electrolyte balance were maintained. The postoperative course was not remarkable. The urinary 17-ketosteroid excretion gradually returned to normal, and the Allen test became negative. The pathological report on the right adrenal was as follows: adrenal cortical neoplasm weighing 6 gm., measuring 3.5×3.5×1.8 cm. The tumor was well encapsulated and showed no definite evidence of invasion. Histological differentiation between adenoma and carcinoma could not be made. The final diagnosis in this case was "adrenogenital syndrome due to benign virilizing tumor" (Fig. 7).

Fig. 6 (Case 2).—Note advanced bone age for child 2 years of age.

TABLE 2.—*Case 2, Adrenogenital Syndrome in a Two-Year-Old Girl* *

Date	Therapy	17-Ketosteroids †	17-Hydroxy-corticoids	Creatinine	Pregnanetriol	Pregnanediol	Allen Test
7-24-57	—	8.3 (a)	1.6	207	0.1	0	Pos.
7-26-57	After cortico-tropin, 6 u. IV×2 days	6.6 (b)	4.2	312.5			Pos.
7-31-57 to 9-29-57	Suppressive corticoid therapy	11.2 (c)	5.7	302.5			Pos.
10-3-57 and 10-16-57	Surgery	Exploration & biopsy of left adrenal Removal of adenoma of right adrenal					
10-16-57 to 1- 9-58	Supportive corticoid therapy	2.3 (d)	5.1	274.9	0	—	Neg.

* Note failure of response in urinary 17-ketosteroids to suppressive doses of corticoids. Urinary 17-ketosteroids fell to normal values and Allen test became negative after removal of tumor.

† (a) represents averages of 2 determinations; (b), 2; (c), 13; (d), 21.

Comment

The 2-year-old child described in Case 2 presented an interesting problem in differential diagnosis. The original impression had been "female pseudohermaphroditism." It was necessary, however, to differentiate between the following possibilities: Cushing's syndrome, adrenarche, female pseudohermaphroditism without adrenal hyperplasia, arrhenoblastoma, congenital adrenal hyperplasia, adrenal tumor.

Cushing's syndrome could be easily discounted because of absence of obvious symptoms such as hypertension, plethora, obesity, "moon face," striae, diabetic glucose-tolerance curve, osteoporosis. The urinary 17-hydroxycorticoids were more or less within normal range (1.7 mg. per 24 hours)[42]; the fasting eosinophil count was 294 per cubic millimeter.

The adrenarche could be eliminated from consideration largely on the basis of the enlarged clitoris, which is rarely found in this disorder, and because of the elevated urinary 17-ketosteroids. In children presenting premature growth of pubic hair (adrenarche) as the chief clinical abnormality, the 17-ketosteroid excretion is usually within normal limits.

Female pseudohermaphroditism without adrenal hyperplasia was also eliminated on the basis of the elevated 17-ketosteroids.

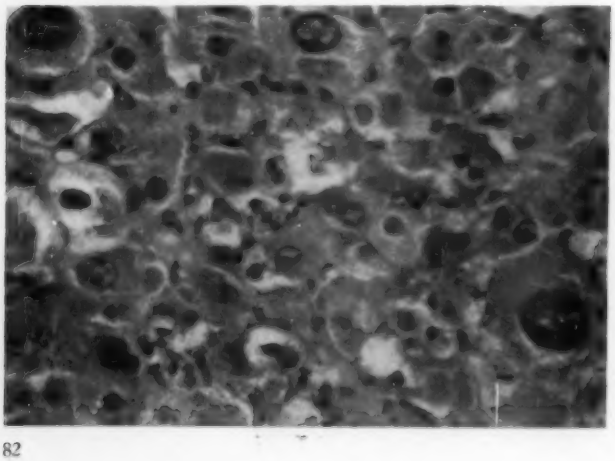


Fig. 7 (Case 2).—Photomicrograph of histologic section of adrenal tumor showing some variation in size of nuclei.

Wilkins[43] reported on a number of girls with definite enlargement of the clitoris at birth. Some of these cases were apparently the result of treatment of the mothers during pregnancy with androgens or progesterone. Others could not be ascribed to any specific factor, but in virtually all of the cases there were no other virilizing features. The presence of hirsutism, advanced growth, and advanced bone age in the child under discussion eliminates consideration of this entity.

Arrhenoblastoma is extremely rare in girls under the age of 15 years. This fact, coupled with the negative findings of a carefully performed rectal examination for pelvic masses, eliminated this disorder from consideration.

There are certain cases in which the diagnosis of adrenal cortical tumor may be made with ease and certainty. Case 1 was such a case. The ability to palpate tumor masses and/or to demonstrate them by x-ray studies in the presence of clinical signs of virilism will permit this diagnosis to be made even in the absence of laboratory studies.

The finding of grossly elevated urinary 17-ketosteroids alone would have been sufficient laboratory evidence to have warranted the certain diagnosis of adrenal tumor in Case 1. The finding of a strongly positive Allen test and high pregnanediol-complex chromogens lent further confirmatory evidence to support the diagnosis of tumor.

Case 2 was not one in which a differential diagnosis between adrenal hyperplasia and adrenal tumor could have been made preoperatively without the use of a series of special studies. There was no palpable tumor, nor could a tumor be visualized by x-ray studies. While the urinary 17-ketosteroid excretion was somewhat elevated for a child of her age (8.3 mg. per 24 hours),[44] it was not so startlingly high (as it was in Case 1, 228.7 mg. per 24 hours) as to immediately suggest a tumor.[45] Repeated urinary 17-ketosteroid assays were within the same range as the values obtained with the initial determinations.

In nearly all cases of virilizing adrenal tumor dehydroepiandrosterone is excreted at a greater rate than in normal persons or in cases of adrenal hyperplasia. The Allen test for dehydroepiandrosterone-like substances is, therefore, an important diagnostic aid.[46] This test may be done as a simple qualitative determination on the same urinary extract that is used for 17-ketosteroid assay, and it should be routinely performed on all patients with elevated 17-ketosteroids. In Case 2 the Allen test was positive on all of the 17 determinations which were run prior to removal of the adrenal tumor. Although an occasional positive Allen test may be seen in patients with adrenal hyperplasia,[47,48] the persistently positive finding was highly suggestive of the presence of a tumor. Quantitative measurements of the color produced by the Allen reaction, when compared against a dehydroepiandrosterone standard, were always considerably above those produced by normal persons. Fractionation of the 17-ketosteroids by a modification of the method of Jayle and his associates[49,50] revealed the 3-β-hydroxy-17-ketosteroids, of which dehydroepiandrosterone is the major component, to be 48.5% of the 17-ketosteroids, as compared to an upper limit of 40% in normal persons. This fractionation served to confirm the results obtained by the qualitative and quantitative Allen tests.

After the institution of suppressive corticoid therapy the fractionation method in use became of little value, since this procedure also measures 11-oxygenated 17-ketosteroids as an individual group. An increase in the 11-oxygenated 17-ketosteroid fraction, which may be produced from the corticoids administered, will automatically lower the relative proportions of the other fractions excreted. Such was the case in this instance. This factor also resulted in the lowering of the percentage of dehydroepiandrosterone-like substances. This was due to the fact that the total 17-ketosteroid excretion increased during corticoid therapy as the result of the inclusion of degradation

products from these administered steroids, and these degradation products were not of the β-configuration. In spite of the relative lowering of the amount of this substance, the qualitative Allen test still remained positive and the quantitative Allen test remained above normal values, although there was a substantial decrease in the percentage output (range, 19% to 41.9%).

The inability of intravenous corticotropin [51] to cause an elevation in 17-ketosteroid output further substantiated the probability that these steroids were being produced by a neoplasm.[44] The inability of glucocorticoids to depress 17-ketosteroid production and dehydroepiandrosterone indicated that these steroids were derived from the neoplasm.[26] Urinary determinations of both of these metabolic products revealed normal or below normal levels (pregnanediol, 0 mg.; pregnanetriol, 0.1 mg. per 24 hours).[38] The absence of abnormal quantities of any of the intermediates in the chain of 17-hydroxycorticosterone synthesis pointed to the diagnosis of adrenal cortical tumor.

Summary

The cases of two children, aged 2 and 3 years, respectively, harboring adrenal tumors are reported. In Case 1 a tumor mass was palpable. In Case 2 the diagnosis was not readily evident.

The urinary hormonal findings which permitted the differential diagnosis in Case 2 were the persistently high 17-ketosteroids and the positive test for dehydroepiandrosterone, neither of which could be suppressed by glucocorticoid administration.

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Primary Arteritis of the Aorta in a Child

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Among the various types of aortic arch syndromes or "pulseless disease," there is a rare primary aortitis with segmental stenosis of the aorta and great vessels, occurring predominantly in women from 20 to 35 years of age.[1] These patients develop progressive narrowing of the aorta and its major branches which results in weakened pulses and low blood pressure in the distribution of the affected vessels. Pathologic examination reveals segmental thickening of the wall of the aorta and its major branches which may be associated with mural thrombosis. Histologically these vessels show a wide variety of inflammatory reactions resembling syphilis, arteriosclerosis, Buerger's disease, periarteritis nodosa, or giant-cell arteritis. The condition has been referred to as Takayasu's disease, "young female arteritis,"[1] and primary arteritis of the aorta.[3] The etiology is unknown. Presented here is the case of a child which seems to fit this category of disease, clinically and pathologically. Cases of this type have not been reported in the pediatric age group. This child presented interesting problems clinically, physiologically, and pathologically, which will be discussed.

Report of Case

A 7½-year-old Negro girl was admitted to Babies and Children's Hospital on March 5, 1957, because of a swollen face and progressive lethargy of one day's duration. The past history revealed four years of intermittent right knee swelling. A diagnosis of synovitis had been made two years previously, when the knee was hot and tender. The patient was treated with heat and salicylates. After the episodic joint swelling had persisted for about a year, a right suprapatellar bursal biopsy was performed which was histologically interpreted as being consistent with rheumatoid arthritis. None of the episodes of joint pain and swelling lasted more than a week, and no other joints became involved. When the patient was seen three months prior to admission in the arthritis clinic, intermittent attacks of headache, abdominal pain, and projectile vomiting had developed during the preceding six months. These were usually followed by three to six hours of sleep. Skull films were reported as normal. Blood pressure in the left arm was also normal at this time. Twenty-four hours prior to admission the patient experienced a typical attack. This was followed by a period of sleep which lasted 18 hours. The mother noted that the child's eyes protruded and that the respirations were irregular. No diplopia, tinnitus, or focal neurologic signs could be elicited. The father died at the age of 36 of a "heart attack," but the mother was living and well. There was no family history of syphilis, tuberculosis, or congenital abnormalities.

On admission to the hospital the patient was semicomatose. Her blood pressures were as follows: right arm, 290/140; left arm, 270/150; left leg, 150/110; right leg, 170/120. Her pulse rate varied from 60 to 150 per minute and was irregular. Her temperature was 96.8 F (36 C). The respirations were 24 per minute and of Cheyne-Stokes character. There was proptosis. Fundoscopic examination revealed bilateral papilledema, arteriolar spasm, retinal edema, and recent retinal hemorrhages. The heart was enlarged to the left. A Grade 1 systolic murmur was heard over the entire precordium. A Grade 2 systolic murmur was heard in the back in the region of the seventh thoracic vertebra. The chest was clear. Aortic pulsations were palpable in the abdomen to the midepigastrium, while below this point no pulsations were palpable. The femoral pulses were present and equal but markedly diminished. The deep tendon reflexes were symmetrical and hyperactive. A positive Babinski sign was present on the right.

Urinalysis showed concentrated urine with many erythrocytes, occasional leukocytes, and a few granular casts. There was 2+ albuminuria. The hematocrit value was 36%. The leukocyte count was 27,000, with 82% neutrophils, 11% lymphocytes, 6% monocytes, and 1% eosinophils. The

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blood urea nitrogen was 18.8 mg. per 100 cc. Roentgenograms of the thorax, skull, and abdomen were not remarkable. An electrocardiogram demonstrated left ventricular hypertrophy.

The administration of 9 cc. of a 50% solution of magnesium sulfate did not produce any reduction of blood pressure. Shortly afterwards two phentolamine (Regitine) tests were performed to exclude pheochromocytoma. Depressions of 80 and 40 mm. of mercury, systolic and diastolic blood pressure, respectively, were noted within three minutes of administration of phentolamine each time, which would indicate a positive test. The depression of blood pressure was associated with an improved state of consciousness. A 3% solution of pentolinium (Ansolysen) tartrate was administered intravenously in an attempt to lower the systolic blood pressure. Two hundred fifty cubic centimeters of this solution was given over a period of one hour before the systolic blood pressure fell below 200 mm. of mercury. Shortly thereafter, the pulse rose to 170 and the blood pressure rose to 270 systolic. The patient became deeply comatose and cyanotic and died after a brief period of slowing pulse and falling blood pressure.

Autopsy Findings.—At autopsy, the gross pathologic findings were confined to the cardiovascular system and brain. The aorta showed a segmental mural thickening which extended from 2 cm. beyond the aortic valve to the level of the renal arteries. The left common carotid, left subclavian, and inferior mesenteric arteries were moderately narrowed by this vascular thickening, while the renal arteries and other major branches were minimally affected. At the level of the diaphragm, the lumen of the aorta was narrowed to a circumference of 0.29 cm. and the wall was markedly thickened (Fig. 1). The constricted segment was 3 cm. long. Beyond the constriction was a 5 cm. segment of poststenotic dilatation. The aortic intima was wrinkled and pitted longitudinally, suggesting the "tree-bark" appearance. Below the level of the renal ostia the aorta was elastic and normal in appearance. The pulmonary artery and circle of Willis were normal. There was moderate cardiac enlargement with preponderant left ventricular hypertrophy (165 gm.; normal, 100 gm.). The coronary vessels were thin-walled and patent. The endocardium and valves were normal. The brain was of normal weight. Small foci of recent hemorrhage were present in the subarchnoid space over the parietal areas bilaterally. The cerebral gyri were moderately flattened, and the sulci, moderately narrowed. In the left parietal region there was an area of softening. Section of this area revealed a 2×3×4 cm. recent intracerebral hemorrhage. The ventricular system was somewhat compressed by diffusely edematous brain tissue. Postmortem blood cultures were negative.

Fig. 1.—Posterior view of en-bloc dissection. The aorta has been opened posteriorly. The descending aorta is thickened, and the area of stenosis is shown as the aorta traverses the diaphragm, (*A*). Distal to the stenosis and above the renal arteries is a zone of poststenotic dilatation (*B*). Immediately inferior to renal arteries (*C*) there is an abrupt transition to normal aorta (*D*).

Microscopic sections from nine different levels of the aorta and its major branches were examined. Histologic changes were limited to that area of the aorta showing gross alteration. The transition between normal and abnormal areas was remarkably abrupt. In the involved segment of aorta, all layers of the wall were involved in a severe chronic inflammatory reaction. The intima was thickened and replaced by nonatheromatous proliferation of fibrous connective tissue. The elastic media was obliterated by focal and confluent areas of exudate composed of plasma cells and lymphocytes (Figs. 2 and 3). Proliferation of blood vessels and fibroblasts accompanied the inflammatory response. The adventitia showed an increase in collagenous connective tissue, with perivascular accumulations of mononuclear cells (Fig. 4). There was marked stenosing, lamellar proliferation of the intima of the vasae vasorum (Fig. 5). The small arteries and arterioles of the brain, adrenal glands, kidneys, and diaphragm showed mild intimal thickening. No hyaline change, vascular necrosis, or perivascular infiltrate was seen in these sites. Sections of the right knee joint capsule showed synovial villi, markedly

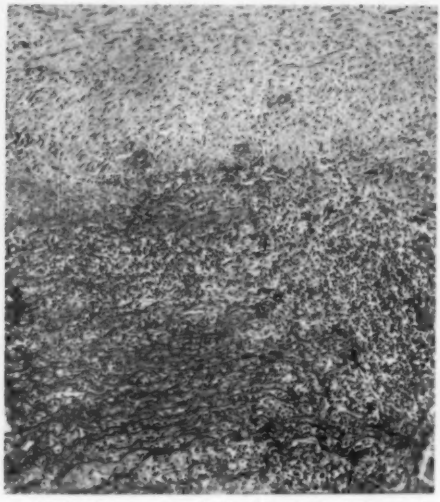


Fig. 2.—Low-power field of aorta in the stenotic area. There is disruption of the elastic fibers, which are replaced by an exudate of round cells. Above is a zone of intimal fibrosis. Hematoxylin and eosin stain.

thickened by the presence of proliferating blood vessels and chronic inflammatory cells. This proliferative form of synovitis is consistent with changes seen in chronic rheumatoid arthritis. Marked cerebral edema and slight endothelial thickening of the cerebral arterioles were consistent with an hypertensive encephalopathy.

Comment

Hypertension, arthritis, central nervous system disease, and hematuria clinically suggested polyarteritis nodosa or some related mesenchymal disease. The apparent multiple system involvement, changing clinical picture, and remittent course made this an important consideration. Seriously considered was the diagnosis of pheochromocytoma. Episodic attacks as described in the history could have been due to adrenal sympathetic crises. It was noted that the phentolamine test was positive several hours before death. The diagnosis of stenosis or coarctation of the aorta was made on the basis of the pressure difference in the arms and legs. The palpable discontinuity of aortic pulsation in the abdomen and the systolic murmur in the back raised the possibility of a constricting lesion of the aorta, distal to the usual site near the left sub-

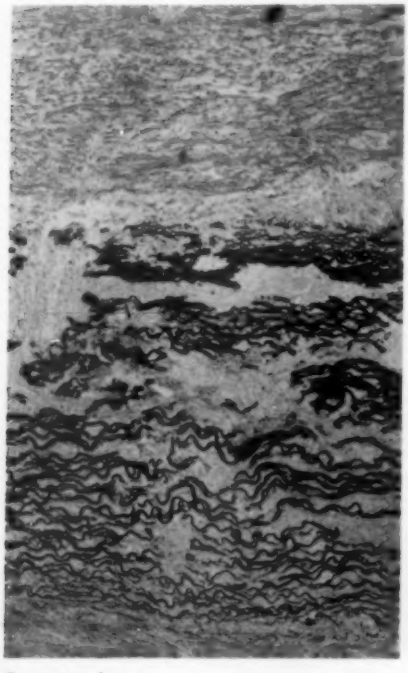


Fig. 3.—Elastic stain of aorta showing disruption and fragmentation of the elastic media. Elastic Van Gieson stain.

Fig. 4.—Low-power field of aorta demonstrating adventitial fibrosis and inflammation. Note the characteristic lamellar sclerosis of one of the larger vasae vasorum. Hematoxylin and eosin stain.

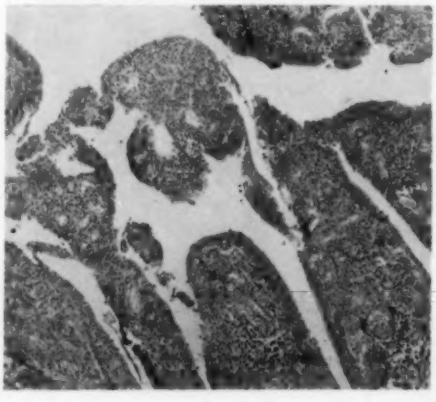
clavian artery. A more inferiorly placed lesion frequently does not cause rib notching because of the more inferiorly placed collateral supply.[4] The findings of progressive lethargy, proptosis, and papilledema suggested an acute hypertensive encephalopathy with increased intracranial pressure.

Stenosis of the aorta was present at the level of the transdiaphragmatic aorta. This site was distal to the usual location of congenital coarctations. The segmental stenosis was associated with marked intimal fibrosis and inflammatory destruction of the media.

Diastolic hypertension resulting from constricting lesions of the aorta is uncommon, according to Griffith et al.[5] Experimentally, Page[6] produced hypertension by creating constricting lesions of the aorta above the level of the renal arteries. When lesions were made below the level of the renals, diastolic hypertension did not result. Page suggested that the hypertension was due to a reduced pulse pressure in the kidneys. He could not demonstrate diminished blood flow. Harrison and Alton,[7] in their experience with the production of hypertension by artificial coarctation in dogs, were unable to confirm Page's suggestion that the hypertension was due to reduced pulse pressure. They state that the cause is unknown. This patient may have developed systolic and diastolic hypertension in both upper and lower extremities in a manner analogous to Page's dogs.

The pathogenesis of the inflammation and segmental stenosis of the aorta remains for consideration. In many ways the lesion resembles syphilitic aortitis, except that aneurysm formation was not present despite marked destruction of the elastica. Negative Kline tests over a five-year period and negative spirochete stains on sections of the involved aorta tended to exclude this diagnosis. Systemic mesenchymal disease with associated arthritis might be considered. Aside from the segment of diseased aorta and knee joint, comparable vascular or inflammatory changes were not present elsewhere. The mild endothelial proliferation observed in the small vessels of the kidney, adrenal, and diaphragm were of the type commonly observed in hypertensive cardiovasular disease. Evidence of fibrinoid degeneration and/or necrotizing vasculitis was not present in the aorta or elsewhere. Granulomatous reaction was not prominent. In view of these facts, a systemic mesenchymal disease might still account for the lesion,

Fig. 5.—Synovia from right knee joint. There is enlargement of synovial villi. Note the increased number of blood vessels and the inflammatory cells within the stroma. Hematoxylin and eosin stain.



although this contention cannot be morphologically supported with any certainty. Definite conclusions as to pathogenesis from the evidence at hand cannot be made. The over-all characteristics of the disease process are similar to those seen in cases categorized as "young female arteritis," or Takayasu's disease.

Summary

A case of constricting primary arteritis of the aorta in a child is reported. The disease process is thought to fit in the category of "young female arteritis," or Takayasu's disease.

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Correction

In the article "Response of Infantile Gastroenteritis to Chloramphenicol," by Y. W. Aboul-Dahab, M. B.; G. S. Tawil, M. B., and S. El-Kholy, M. B., in the September issue of the JOURNAL, page 348, Dr. Aboul-Dahab was identified as *ancien élève de l'Institut Pasteur (Paris);* Dr. El-Kholy should have been so identified. The last sentence of the third paragraph under the heading Conduct of Investigation, page 349, should read: "During Period III a few infants' mothers insisted on discharge before the end of the requisite follow-up; arrangement was made for most of them to be seen as outpatients." The second sentence of the paragraph under the heading Treatment page 349, should read: "In severer cases this was supplemented by subcutaneous infusion (often with hyaluronidase) for a few days."

Case Reports

Paroxysmal Nocturnal Hemoglobinuria in a Negro Child

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Hemolytic disease in childhood is frequently obscure in etiology and difficult to classify. Recently we have seen such a case in a 9-year-old Negro girl, which subsequently proved to be paroxysmal nocturnal hemoglobinuria (PNH) and which is reported in some detail not only because of its rarity in childhood but also because of the dearth of cases in the literature of PNH in Negroes. To our knowledge it has not been reported previously in a Negro child.

Report of Case

The patient is a 9-year-old Negro girl whose birth and infancy were normal. There is no family history of anemia, and there are three siblings living and well, one additional sibling having died at nine months of age from dysentery.

The child was seen in the pediatric clinic of the Indianapolis General Hospital at 5 years of age because of nasopharyngitis, with frequent subsequent visits because of upper respiratory infections and tonsillitis. A tonsillectomy was done when the patient was 7 years old. A year and a half later the child was seen in the ophthalmology clinic because of "headaches and blackout spells after reading"; the eyes were found to be normal. Six months later, at the age of almost 9 years, the patient was admitted to the General Hospital because of severe frontoparietal headaches of six weeks duration, with some difficulty in walking during the prior 24 hours. The only definite findings on physical examination were weakness of both right extremities and loss of the superficial reflexes on the right.

The red blood count was 3,450,000/cu. mm., the hemoglobin level, 3.6 gm/100 ml. blood, and the red blood cells were hypochromic. The white cell count was 5250/cu. mm. with a normal differential. The reticulocyte count was 3%, with a platelet count of 122,000/cu. mm. (normal, 150,000-300,000). The sickle-cell test and the direct and indirect Coombs' tests were negative. The serum bilirubin was 2.1 mg/100 ml. blood total with a one minute direct reacting level of 0.1 mg. Examination of the spinal fluid revealed no abnormalities. A bone marrow examination revealed erythroid hyperplasia. X-rays of the skull, cervical spine, chest, and pelvis were interpreted as normal. A carotid angiogram was noninformative, and electroencephalograms on several occasions revealed evidence of a focal disturbance in the left frontal area. A pneumoencephalogram revealed partial filling of the ventricular system with some cortical collection of air in the sulci on the left side, which was interpreted as possible cortical atrophy.

The patient was given several blood transfusions, and the abnormal neurological signs returned to normal. On discharge from the hospital, the child was placed on a liquid iron medication.

Three months later the patient was readmitted to the hospital for reevaluation. Fatigue was present, and a mild icterus had been noted recently. The liver was palpable 2 cm. below the right costal margin: the remainder of the physical examination was normal.

There was now a pancytopenia, with 7.2 gm. of hemoglobin per 100 ml., 4950 white blood cells and 90,000 platelets/cu. mm. blood. The tourniquet test was negative. The urine showed only a faint trace of albumin. The serum protein and A/G

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From Indianapolis General Hospital.

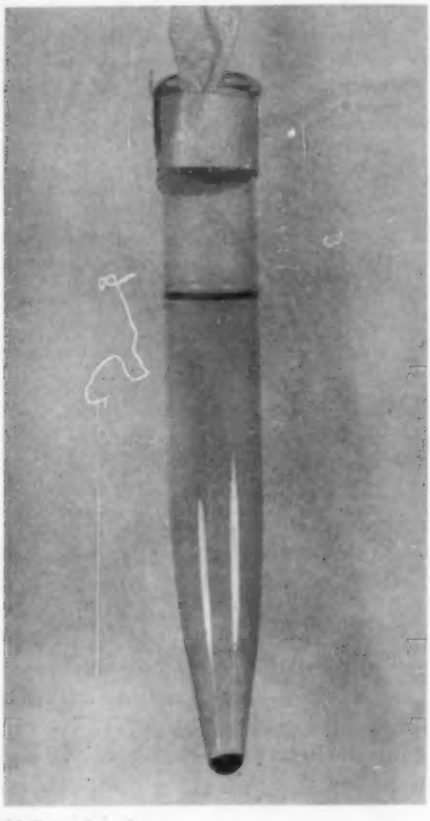
Mrs Frances Blackford, M.T. (A. S. C. P.), the Department of Illustration, Indianapolis General Hospital gave technical assistance, and Dr. Herbert F. Call, Chairman of the Pediatric Department, Indianapolis General Hospital gave permission to publish this case report.

Assistant Pathologist, General Hospital, and Assistant, Department of Pathology, Indiana University Medical Center (Dr. McDougal); Clinical Pathologist, General Hospital, and Assistant Professor, Indiana University Medical Center (Dr. Shively), and Resident in Pediatrics, General Hospital and Indiana University Medical Center (Dr. Palmer).

ratio and other liver function tests were normal, except for an elevated bilirubin of 2.5 mg. with a one minute direct reacting level of 0.2 mg/100 ml. blood and a sulfobromophthalein sodium (Bromsulphalein) retention of 10% in 45 min. The erythrocytes were normochromic now, the iron deficiency having been corrected by the transfusions and the oral iron. The osmotic fragility test was normal at this time. The Coombs' tests were negative, as were tests for atypical agglutinins, using trypsinized red cells at 4, 25, and 37 C. The alkali denaturization test and electrophoretic examination of the patient's hemoglobin revealed A hemoglobin with 28% F. The sickle-cell test was again negative.

During her hospitalization, there was an episode of slurred speech, "being asleep on the left side," left facial weakness, and labored respirations. It was felt that the patient was having a hemolytic crisis, and she was transfused with whole blood. Because of the unclassified hemolytic anemia, a splenectomy was performed, with the removal of three additional accessory spleens. The spleen weighed 70 gm. (normal weight for a child her age), and there were neither gross nor microscopic abnormalities. Postoperatively, the patient developed a suture abscess, urinary tract infection, and pneumonia.

Fig. 1.—Rous' test for hemosiderin in the urinary sediment. The sediment is stained a deep blue-green color (Prussian Blue reaction).



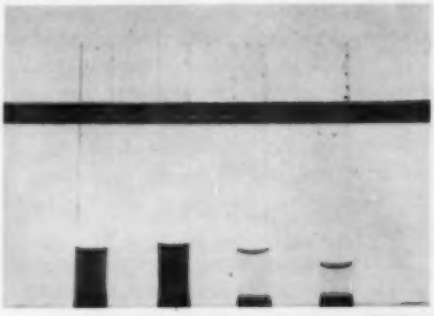


Fig. 2.—The Crosby thrombin test. All four tubes contain type-compatible serum from a normal control. The second and fourth tubes (from the left) contain added thrombin. The two tubes on the left contain the patient's cells, the two on the right, control cells. There is hemolysis in the two tubes containing the patient's cells, with more hemolysis in the tube containing added thrombin.

Because of the persistent anemia which was refractory to treatment, the patient was readmitted in a few months for further study. Because of the unclassified hemolytic anemia, associated with leukopenia and thrombocytopenia, and a marked erythroid hyperplasia of the bone marrow, studies for the diagnosis of (PNH) were done, confirming the diagnosis.

The urine was positive for hemosiderin (Rous' test, Fig. 1) and hemoglobin (occult blood), although no intact red blood cells were seen. Both Ham's presumptive and complete tests for acid hemolysins[3] were positive, as well as the Crosby thrombin test (Fig. 2).[2] The serum hemoglobin, tested by the Crosby method[4] was elevated, 65 mg/100 ml. serum. The fecal urobilinogen was elevated for a child.

The patient has continued to be moderately anemic (8 to 9 gm. of hemoglobin per 100 ml. blood) and to have nucleated red blood cells in the peripheral blood. Two mild transient episodes of paresthesia in the lower extremities have occurred but otherwise the patient enjoys fairly good health and attends school.

Comment

Paroxysmal nocturnal hemoglobinuria (PNH) has been described by Crosby[4] as "a disease of the hematopoietic sys-

tem manifested by chronic hemolytic anemia, leukopenia and thrombocytopenia . . . In addition to anemia the patients are frequently afflicted by recurrent infections, especially of the respiratory and urinary systems, by headaches and bouts of abdominal pain, and by venous thromboses in the extremities, the brain, and the portal system."

PNH is an acquired hemolytic anemia in which the cells are defective,[5] alike in this regard only to pernicious anemia. The nature of the defect is unknown, although it is thought to be a "defect of stromal protein which renders it liable to proteolytic activity of PNH hemolytic enzymes."[5] Some claim to have shown a stromal deformity in the PNH erythrocyte on electron microscopy,[6] but others find no such abnormality.[7] Whatever the defect is, it is apparently shared by leukocytes and platelets, for a pancytopenia is usually seen as was present in the patient presented. The thrombocytopenia may be due to the tendency of the platelets to agglutinate, which may also explain the tendency toward thromboses in the patients. In fact, the leading causes of death in PNH are portal or hepatic thromboses, anemia, and cerebral thrombosis.[5] The frequent bouts of pain that these patients have, as well as cerebral thromboses, are probably due to this thrombotic tendency. Our young patient has already had several attacks of what appear to be transient cerebral thromboses.

As the hemolysis in PNH occurs intravascularly rather than in the cells of the reticuloendothelial system, as in most other hemolytic anemias, there is a rather constant hemoglobinemia.[8] Any amount greater than 5 mg. % is considered abnormal, and the renal threshold is about 130 mg/100 ml. serum.[8] Some of the hemoglobin spills into the urine, producing positive Hematest or benzidine tests in the absence of red cells. The rest is broken down by the renal tubular epithelial cells into heme and globin, and the heme is further broken down into bilirubin, ferritin, and hemosiderin. These cells are poorly fitted for such work and, filled with hemosiderin, soon slough off. These cells may be found in the urinary sediment and can be stained by the Prussian blue reaction in Rous' test (Fig. 1). This represents a considerable loss of iron, and it explains why these patients show only small amounts of iron present in the reticuloendothelial cells, for example, in the bone marrow, in contrast to other hemolytic anemias.

In a patient with an unclassified hemolytic anemia, the diagnosis of PNH may easily be established by first using screening tests, and then definitive tests. Ham's presumptive test[1] consists of placing whole blood from the patient and a normal control into sterile corked tubes and incubating these at 37 C for 6 to 24 hours. Enough acidity is produced to cause hemolysis of PNH cells, although there may be hemolysis in other hemolytic diseases. There should be no hemolysis in the control tube. If this test is positive, and if there is hemosiderin and possibly hemoglobin in the urine, the Crosby thrombin test (Fig. 2)[2] and the complete Ham's test[1] for acid hemolysis should be performed. The former consists of the following procedure: Acidified compatible control serum is placed in each of four tubes, the patient's cells in two and the control cells in two; thrombin is added to one tube of patient's cells and one tube of control cells. There should be no hemolysis in the control tubes but some hemolysis in the patient's tubes, more occurring in the tube with the added thrombin. The Ham's test involves more controls and includes a duplicate series of tubes using both patient's and control cells and patient's and control sera. The sera are treated as follows: 1. left unaltered; 2. acidified; 3. acidified and heated (56 C), and 4. acidified, heated, and then fresh guinea pig complement is added. Only Treatments 1 and 2 should produce hemolysis of PNH cells, with more hemolysis in the second case than in the first.

The spleen is usually normal in this condition and, although it is frequently removed by those clinicians who feel that the spleen should be removed in most cases of hemolytic anemia (as was done to our patient), its removal produces no improvement. On the contrary, because of a very high mortality rate (24%)[4] associated with splenectomy in this disease in the literature, splenectomy is definitely contraindicated.

The lability of the platelets and the apparent relationship of thrombin to the hemolytic process led to a theory of the etiology of PNH,[9,10] as well as a specific test, the Crosby test. Thrombin was thought to inactivate a serum inhibitor of the PNH system more rapidly than it inhibited a hemolytic factor, thus accelerating hemolysis in an acid medium. This theory has led to the use of bishydroxycoumarin (Dicumarol) in the treatment of PNH with occasional symptomatic success.

Recently much work has been done to define the factors in normal human serum which hemolyse PNH cells. Both Harris[11] and Crosby[10] state that the magnesium ion is essential to the reaction and that the other factor resembles but yet differs from complement.[12] Guinea pig serum, when added to the mixture of test cells and heated serum (56 C for 30 min.), will not cause hemolysis,[1] a differential point in the Ham test, but will increase the hemolysis caused by normal serum or by sera which are deficient in the third and fourth components of complement.

In announcing the discovery of the properdin system in 1954, Pillemer[13] stimulated additional investigation of the etiology of PNH. Properdin is a heat-labile euglobulin[14] found in the sera of most animals including "germ free rats." Properdin, plus all four factors of complement and magnesium, is the agent which hemolyses the PNH erythrocytes.[15] It is of interest to note that thrombin preparations contain a large amount of properdin,[16] and thus can restore to properdin-deficient sera hemolytic ability and can increase the hemolysis of normal sera.* This increase is the basis of the Crosby thrombin test,[2] while properdin may be the heat-labile hemolytic factor of Crosby.[16]

The identification of properdin as the hemolytic factor of PNH may well have great clinical significance for two reasons: 1. it may explain the plasma transfusion reaction often seen in these patients, and 2. it may lead to a rational means of blocking the hemolytic factor in vivo. It is known that zymosan and other polysaccharide compounds, such as the dextrans, interact with and inactivate properdin and the third component of complement.[15] Large amounts of substances that interact with the properdin system decrease the serum properdin level while small amounts increase it. The serum properdin level of PNH patients in a hemolytic crisis is usually quite low,[17] perhaps indicating an interaction between PNH cells and properdin. The administration of dextran during a hemolytic crisis with PNH has been reported to be of some help in controlling these episodes,[18] and further evaluation of this substance in PNH may not only be of value in the treatment of this disease but may also clarify its pathogenesis.

Summary

A 9-year-old Negro girl is described, with symptoms of chronic anemia, leukopenia, and thrombocytopenia, and transient but severe signs and symptoms of cerebral damage (headaches, paresthesias, and hemiparesis). The anemia was shown to be hemolytic by the marked erythroid hyperplasia of the bone marrow, the presence of hemoglobin (occult blood) and hemosiderin (Rous' test) in the urine, and by elevated levels of serum hemoglobin, bilirubin, and fecal urobilinogen. The Coombs' test and tests for sickling, osmotic fragility, and atypical agglutinins were negative or normal. The Ham tests and the Crosby test for paroxysmal nocturnal hemoglobinuria (PNH) were positive.

* For a more recent concept, see the Addendum, page 96.

Splenectomy is of no value in the treatment of this disease and is actually contraindicated. We feel that performing splenectomies for undiagnosed hemolytic diseases is often unjustified.

Plasma transfusions may aggravate the hemolytic process; consequently washed red blood cell transfusions should be given if transfusions are needed.

The substance in serum or plasma which hemolyzes the PNH cells appears to be properdin, a naturally occurring euglobulin. The possibility of using dextran is suggested.

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Addendum

Since this paper was submitted for publication, Hinz [19] has restudied the properdin content of thrombin preparations and found that there is none present. Crosby [20] has also prepared properdin-free thrombin and thromboplastic reagents which still hemolyze PNH red cells. Thus the relation of the clotting mechanism to the hemolysis of PNH red cells is still unsettled.

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Congenital Choledochal Cyst

Demonstration by Oral Cholecystography

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Demonstration of a choledochal cyst by means of oral cholecystography has not been reported in the American medical literature until recently. Moseley [1] presented the first case so demonstrated. The patient was a 5-year-old white girl. More recently, Paulino,[2] of Rio de Janeiro, reported a case in a 22-year-old woman. To my knowledge, the case herein presented is the third to appear in the American literature. As in the original case, the patient is a child.

Report of Case

A 13-year-old Negro boy was admitted to St. Joseph Mercy Hospital on June 8, 1957, as a patient of Dr. Richard W. Deatrick. For the preceding six days he had been having colicky epigastric and periumbilical pain. He had vomited intermittenly during this period. The urine was described as "dark yellow." Enemas had revealed "gray" stools.

The past history revealed similar attacks of abdominal pain since the age of 5 years. On several occasions he had an elevated serum bilirubin. His first bout of visible jaundice occurred at the age of 5 years. The child had been studied at several hospitals on a number of occasions during the previous eight years, and to my knowledge a diagnosis had never been established. I do not know of any previous cholecystograms. On one occasion a study for sickling had been negative.

The physical examination at the time of admission revealed a young Negro boy in no acute distress. The vital signs were normal. The liver was palpable 2 fingerbreadths below the right costal margin. There was no tenderness to palpation.

Pertinent laboratory findings were as follows: The white cell count was 16,100, with 85% segmented forms. No bile was found in the urine, and the urobilinogen was in normal dilution. The serum cholesterol was 244 mg. %. The icterus index was 15. The cephalin flocculation was negative both at 24 hours and at 48 hours. Total serum bilirubin was 2.7 mg. % after initial readings of 1.9 mg. % at 10 minutes and 2.0 mg. % at 30 minutes.

Fig. 1.—Oblique view showing most of the contrast agent in the ascending colon. Only very faint opacification of a large ovoid structure in the right upper quadrant of the abdomen occurs.

A film of the abdomen on June 8 was negative. An oral cholecystogram on June 11 (Fig. 1) shows faint opacification of a large round structure in the right upper quadrant of the abdomen. Most of the contrast agent was in the ascending colon. The gallbladder could not be identified. A repeat oral cholecystogram on June 12, with use of the same amount of iopanoic acid (Telepaque) as on the previous day's study, showed opacification of two structures in the right upper quadrant of the abdomen (Figs. 2 and 3). The most lateral of the two structures was tubular in shape and contracted well after a fatty meal was given. The cystic duct could be identified at the proximal end of it. The medial opaque image was roughly ovoid in shape, measured 3.5×4.5 cm., and showed no contraction following stimulation by the fat meal.

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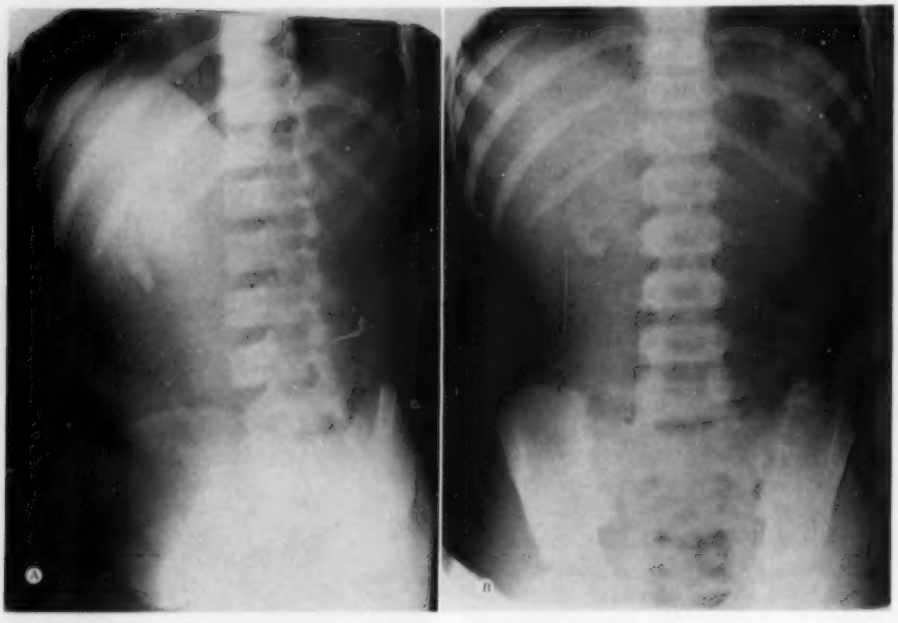

Fig. 2.—*A*, posteroanterior, and *B*, oblique views one day later, after ingestion of a similar amount of iopanoic acid, now show good concentration of contrast agent within the gallbladder and better opacification of the cyst, which lies medial to the gallbladder.

The tubular structure could not be identified on a film taken four hours after the fat meal, but there was very faint visualization of the larger ovoid structure. On the basis of this study the possibility of a choledochal cyst was postulated.

The patient was discharged on June 13 and was readmitted to the hospital on July 1 for surgery by Dr. Clarence E. Crook. The surgical note indicates that the gallbladder was long and slender. The cystic duct merged into a convoluted somewhat flabby cyst-like cavity which held at least 3 oz. of fluid when distended. This cyst lay between the lower surface of the liver and the posterolateral aspect of the first and second portions of the duodenum. It yielded yellow bile when aspirated. Probe patency between the cystic duct and the cyst was established, and, although it seemed likely that the common duct might be connected to the cyst at the same opening as the cystic duct, this was not specifically demonstrated at operation. The cyst was anastomosed directly to the second portion of the duodenum. A No. 15 polyethylene tube was inserted into the dome of the gallbladder in order to permit later study by means of roentgenography. Recovery was uneventful, and the patient was discharged from the hospital 10 days after the operation. Seven weeks after the operation a cholangiogram was obtained

Fig. 3.—A film taken after the fat meal shows good contraction of the gallbladder, better visualization of the cystic duct, and continued opacification of the cyst, which does not contract.

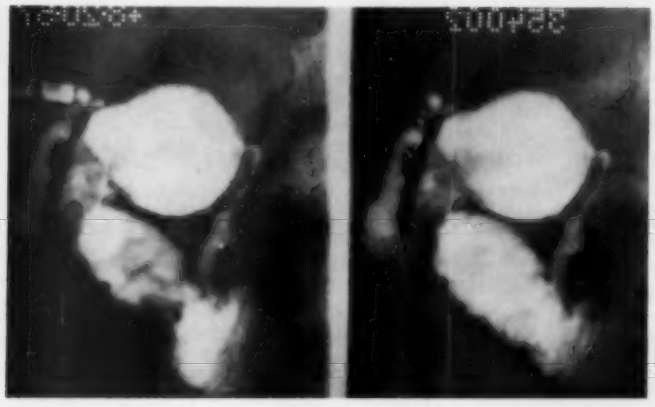

Fig. 4.—Two spot films obtained seven weeks after surgery show the relations between the gallbladder, choledochal cyst, biliary ducts and duodenum. The polyethylene tube is inserted into the gallbladder.

by means of injection of dye through the polyethylene tube. Spot films (Fig. 4) taken at this time demonstrate the relationships between the duodenum, the choledochal cyst, the biliary ducts, and the gallbladder.

Comment

The first case of a congenital cyst of the biliary tree was reported by Vater, in the early part of the 18th century. In the past 25 years, several reviews of the subject have been published and approximately 250 cases have been reported. These cysts are congenital in nature; they predominate in the child and young adult (75% of the patients are less than 25 years of age), and they appear more frequently in females than in males.

My purpose in presenting this case is not to review the literature with regard to etiology, pathology, and treatment of this condition but to emphasize that the cyst may be visualized on occasion by means of oral cholecystography. Cantey,[3] in a recent publication on the subject, does not so much as mention roentgenography as a diagnostic adjunct. Moseley,[1] in his article, indicated that, apart from lack of opacification of the cyst itself, all other cases in which oral cholecystography had been used failed to show opacification of the gallbladder, except for one case reported by Wright in 1935.

In the past, roentgenographic procedures which have been of aid in demonstrating the cyst prior to surgery include (*a*) introduction of contrast material into the cyst by means of needle puncture; (*b*) gastrointestinal series, which may show secondary pressure defects on neighboring structures, and (*c*) intravenous pyelography, which may show a right hydronephrosis due to pressure of the cyst on the right ureter. Intravenous cholangiography has been no more successful than oral cholecystography in revealing the lesion. Characteristics of an occasional cyst which aid in its demonstration include calcification of the cyst wall and gas within the cyst. The latter is a rare finding. McLaughlin[4] considers it of utmost value in making the diagnosis. Occasionally, a cystic tumor may be seen on a plain film of the abdomen. At the time of operation the diagnosis can be established by operative cholangiography.

The differential diagnosis includes hydatid cyst, pancreatic cyst, congenital cysts of the liver, hydrops of the gallbladder, mesenteric cyst, retroperitoneal tumors, and intestinal duplication.

Tsardakas and Robnett[5] indicate the importance of preoperative recognition of the lesion as it affects the morbidity and mortality rates. They state, "The crux of the matter (in so far as morbidity and mortality in the operated cases is concerned) is the preoperative recognition of the disease."

Moseley[1] suggests that the use of iopanoic acid may have been a contributing fac-

tor in visualization of the cyst in his case. In the present case, while iopanoic acid was also used, it should be noted that the initial study was not successful in showing the cyst to advantage, while a repeat study on the following day, with use of the same amount of dye, was effective. Paulino[2] does not indicate what contrast substance he used.

Summary

A case of congenital choledochal cyst in a 13-year-old Negro boy, visualized by means of oral cholecystography, is presented. I believe that this is the third such case to be reported in the American medical literature.

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Clinical Notes

Esophageal Stricture from Accidental Ingestion of Clinitest Tablets

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Ingestion of lye is a well-known cause of chemical burns and stricture of the esophagus. Approximately 50% of such burns and almost all strictures result from the ingestion of this agent. Owens,[1] in reviewing 131 cases of chemical burns of the esophagus, found lye to be the cause of 65 cases. Of 20 cases of stricture, this substance was ingested in every case in his series. Similarly, Stothers [2] found 22 of 47 cases of chemical burns of the esophagus to be due to lye. Of 18 strictures in his group, 12 were due to sodium hydroxide.

Clinicians may not be aware of the commonly used agents found in the home which may contain lye. One which we would like to describe is "Clinitest," the tablets almost universally used by diabetics in their daily urine testing. These tablets contain a combination of anhydrous sodium hydroxide, copper sulfate, citric acid, and sodium bicarbonate. When added to a solvent, boiling is produced by the heat of solution of the anhydrous sodium hydroxide and by the neutralization reaction between sodium hydroxide and citric acid. If this tablet is accidentally ingested, the heat produced, in addition to the caustic action of the lye, can cause a thermal and chemical burn with resultant scarring and stricture. These changes are probably augmented somewhat by the astringent and irritant effects of the contained copper sulfate. The case reported here is illustrative.

A 3½-year-old Puerto Rican girl was admitted to the Bronx Municipal Hospital Center on Aug. 6, 1957. The patient began vomiting intermittently three weeks prior to admission, about one week after a visit to her maternal grandmother, a diabetic. This vomiting progressed, as did anorexia and weight loss, until the day of admission, when the patient vomited everything ingested. The vomitus was nonbloody and consisted of partially digested food. Physical examination was nonrevealing. On the third hospital day the grandmother volunteered the information that the patient had swallowed a Clinitest tablet which was accessible and used daily in urine testing. On the fourth hospital day an esophagram (Fig. 1) revealed a stricture of the esophagus just above the level of the carina. Esophagoscopy showed the stricture, and a tube gastrostomy was done.

Fig. 1.—Esophagram on admission. There is a 1 cm. segment of persistent narrowing with proximal dilatation and tapering.

On Sept. 20, 1957, a repeat esophagram (Fig. 2) showed complete obstruction at the stricture site. On Jan. 10, 1958, after unsuccessful attempts at dilatation, the stenotic segment was resected and an end-to-end anastomosis was performed. Dilatation proximal to the stricture was noted. The resected segment measured 6 mm. in length and revealed a markedly narrowed esophageal lumen (Fig. 3). Microscopic study showed fibrosis of

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Fig. 2.—Esophagram one month after Figure 1. Obstruction is now complete, with increasing proximal dilatation and tapering. The trachea is displaced anteriorly by the dilated esophageal segment.

Fig. 3.—Resected segment. The slit-like esophageal lumen measures 0.4 cm. in greatest diameter.

Fig. 4.—Esophagram four weeks after surgery. There is still slight narrowing and residual proximal dilatation at the anastomotic site. The swallowed opaque material passes easily.

the submucosa and serosa, associated with muscle hypertrophy.

Four weeks after surgery the patient was eating strained bulky foods. An esophagram (Fig. 4) at this time showed easy passage of the opaque material.

Comment

In 60% of the cases[3] of sodium hydroxide ingestion, a single segment of the esophagus above the tracheal bifurcation is involved. In the remaining cases the region affected is usually either a solitary area in the distal esophagus or multiple sites.

Pathologically, an initial diffuse mucosal edema, a few hours after ingestion, is followed by a stage of necrosis in 24 hours. Sloughing of necrotic material occurs at the end of the first week, and repair fibrosis, with stricture as a complication, is seen after the third week. Clinically, an initial period of discomfort is followed by a "silent" interval; subsequent severe dysphagia occurs within a month in 60% of the cases.

Four cases of Clinitest esophageal stricture have previously been recorded in the literature. Canby's[4] two cases were children 3 years and 6 weeks old. Bloomer and Kirchner's[5] case was a 14-year-old

diabetic girl. The patient mentioned in Owens' report is classified only as an "adult."

In Owens' case, the stricture was at the level of the cricopharyngeus muscle and a congenital narrowing was thought to be present which held the tablet at this site. In the other cases, the stricture was located at the level of the third dorsal vertebra, the sixth dorsal vertebra and the "aortic arch."

One case was associated with an esophageal ulcer extending 1 cm. posteriorly from the lumen of the stricture. Dysphagia, severe enough to cause hospitalization, developed within three to five weeks in each case.

Summary

Accidental ingestion of tablets used by diabetics for testing urine (Clinitest tablets) can cause a partial or complete stricture of the upper esophagus because of the action of the lye constituent. The contained copper sulfate may also play a secondary role. A case of complete stricture from Clinitest ingestion is reported.

Of four previously recorded cases, three have been in children. One of these also had a complete stricture.

An esophagram will confirm the clinical impression of esophageal stenosis or stricture. If the patient has contact with a diabetic and no etiology is apparent, ingestion of Clinitest should be considered.

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Addendum

Since this paper was submitted, Tomsovic and Javid[6] have reported an additional case of esophageal stricture from "Clinitest" ingestion in a 5-year-old child.

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Abstracts from Current Literature

Acta pædiatricia, Stockholm

Abstracted by William W. Cleveland, M.D.

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Hemolytic Episodes as the Cause of Jaundice in Children with Allergic Disease—"Allergic Jaundice." M. Barr, S. Kraepelien, and R. Zetterström.—p. 113.

Infectious Mononucleosis and Pseudomonucleosis in Childhood. B. Vahlquist, H. Ekelund, and E. Tveteras.—p. 120.

Early Diagnosis of Gonadal Dysgenesia (Turner's Syndrome). M. Andersson, L. Bjersing, and S. Rafstedt.—p. 132.

Ellis-Van Creveld Syndrome: Report of Two Cases in Siblings. F. N. Mitchell and W. W. Waddell.—p. 142.

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Aimed Antibiotic Treatment of Pneumonia on the Basis of Tests Carried Out with Subglottic Swabs. B. Steiner, G. Putnoky, K. Kovács, and J. Szabon.—p. 172.

* Importance of the Quantitative Determination of Direct and Indirect Bilirubin in Hemolytic Disease of the Newborn. V. Jirsová, M. Jirsa, and M. Janovsky.—p. 179.

Importance of the Quantitative Determination of Direct and Indirect Bilirubin in Hemolytic Disease of the Newborn.—On the basis of data obtained by serial measurements of direct and indirect bilirubin levels in 32 infants with erythroblastosis the authors discuss the relative importance of these two fractions in this disorder. It is postulated that two principal mechanisms are involved in the excretion of bilirubin by the liver; first is the conversion of indirect to direct bilirubin by conjugation with glucuronic acid, and second is the excretion of this conjugate by the liver into the biliary tract. It is, therefore, pointed out that various clinical pictures may result from erythroblastosis, depending on the extent of involvement of these systems. In the usual case of hemolytic disease, in which the elevation of bilirubin is predominantly of the indirect fraction, it is suggested that an inadequate capacity for conjugation of indirect bilirubin is present, while in the more severe types, in which the direct fraction of bilirubin is elevated early in the disease, inadequacy of both conjugation and excretion is presumed. The prognostic and therapeutic implications of these concepts are discussed, and it is urged that careful measurements of both fractions of bilirubin be done routinely. In addition, a preliminary report of the use of thiocapryllic acid in the management of two severe cases of erythroblastosis is involved.

Comment: Because of current interest in erythroblastosis stimulated by newer knowledge of bilirubin metabolism, the concepts presented here seem worthy of review. The apparent response of two patients to thiocapryllic acid admittedly has little significance in itself, but this stimulates us to look forward to further reports of the use of this material, which presumably will be forthcoming from these authors.

American Journal of the Medical Sciences, Philadelphia

Abstracted by Robert A. Aldrich, M.D.

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Paradoxical Values of the Erythrocyte Sedimentation Rate in Rheumatic Fever: A Comparison Among Three Acute Phase Tests. T. N. Harris, Sidney Friedman, and James Tang.—p. 259.
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* The Production of Antibody by Splenectomized Persons. Ralph M. Myerson, Robert Stout, and W. Paul Havens.—p. 297.
The Clinical Significance of Alterations in Lactic Dehydrogenase Activity of Body Fluids. Felix Wroblewski.—p. 301.
Pathology and Bacteriology—Giant Cell Tumor of Bone. William Anderson.—p. 334.

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Needle Biopsy of the Parietal Pleura in Tuberculosis. William Weiss.—p. 431.
The Adrenogenital Syndrome "Virilizing Type" in an Adult Male: A Case Report. William H. Perloff and Harry E. Hadd.—p. 441.
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* Changes in Serum Pseudo-Cholinesterase Levels in Patients with Diseases of the Heart, Liver, or Musculoskeletal Systems. Charles B. Moore, Robert Birchall, Harold M. Horack, and Hugh M. Batson.—p. 538.
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Angiocardiographic Glimpses of Cardiac Physiology. Melvin M. Figley.—p. 613.
Paper Electrophoretic Partition of Serum Protein and C-Reactive Protein in Patients with Bronchiectasis with a Preliminary Report on the Effect of Prolonged Antibiotic Treatment. Kenneth L. Vosti, Joyce Z. Pearson, Mark H. Lepper, Harry F. Dowling, and George G. Jackson.—p. 656.
Clotting Factor Assays on Plasma from Patients Receiving Intramuscular or Subcutaneous Heparin. Samuel I. Rapaport and Sara Beth Ames.—p. 678.
Differences in Plasma Total Base and Cations in Severe Renal Disease. Makepeace U. Tsao, Jeana Levinthal, Lillian J. Wyngarden, Charles H. Sloan, and Shirley S. Sethna.—p. 696
Pediatrics—Studies on Elliptocytosis: I. Hereditary Elliptocytosis in the Pediatric Age Period; A Review of Recent Literature. Irving J. Wolman and Ayse Ozge.—p. 702.

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Phenolic Compounds in Chemotherapy of Rheumatic Fever. Norman E. Clarke, Charles N. Clarke, and Robert E. Mosher.—p. 7.
Host Factors Affecting Growth of B-Hemolytic Streptococcic in the Human Pharynx: A Pilot Study. W. W. Schottstaedt, James H. Krause, David W. Foerster, Robert T. Dooley, and Florene C. Kelley.—p. 23.
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A Comparison of Penicillin G and Penicillin V in Treatment of Streptococcal Sore Throat. Norbert Schalet, Bernard M. Reen, and Harold B. Houser.—p. 183.

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The Etiology of Common Respiratory Infections in a Civilian Adult Population. Hans G. Grieble, George G. Jackson, Harry F. Dowling, Delores H. Seketa, and Truman O. Anderson.—p. 245.
Amebiasis as Seen in an Office Practice. R. Bretney Miller.—p. 261.
* Electroencephalographic Correlation of Laughing Fits. Andre A. Weil, W. A. Nosik, and Nicholas Demmy.—p. 301.

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Cushing's Syndrome Produced by Normal Replacement Doses of Cortisone in a Patient with Defective Mechanism for Steroid Degradation. John E. Howard and Claude J. Migeon.—p. 387.
Lactic Dehydrogenase and Glutamic Oxaloacetic Transaminase in Normal Pregnant Women and Newborn Children. Michael West and Hyman J. Zimmerman.—p. 443.
Classic Hemophilia in a Negro Infant.—Paul W. Boyles and Jane Currie.—p. 452.

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* Clinical and Microbiological Aspects of Salmonellosis. George M. Eisenberg, Leonard Brodsky, William Weiss, and Harrison F. Flippin.—p. 497.
The Effect of Ammonium Chloride Induced Maternal Acidosis on the Human Fetus at Term: II. Electrolytes. Irwin H. Kaiser and Robert C. Goodlin.—p. 549.
Therapeutics—Antimicrobial Therapy: The Concurrent Administration of Two Drugs. Ralph Tompsett.—p. 585.

235, No. 6 (June) 1958

* The Effect of Meprobamate (Equanil) on Brain-Damaged Patients. C. H. Carter.—p. 632.
Pediatrics—Intraperitoneal Blood Transfusions. Paul Mellish and Irving J. Wolman.—p. 717.

Fibrinogen Concentrations in Various Clinical Conditions.—The authors have made observations on the fibrinogen levels in adult patients with a variety of vascular cardiac disorders. Included are data on children with acute rheumatic fever, and there are also a few observations on patients with liver disease.

It would appear that in acute rheumatic fever the fibrinogen level is elevated during the acute phase of the rheumatic process and declines with the clinical activity of the disease. This clinical test may be of value in the study of acute rheumatic fever in much the same way that serum mucoproteins and C-reactive proteins have been used in the past.

The Number of Blood Cultures Necessary to Diagnose Most Cases of Bacterial Endocarditis.—Studies were made on bacteriologically proven cases of bacterial endocarditis. All but three of the patients were over the age of 20 years. Blood samples were obtained by venepuncture; 5 ml. of blood was injected into 20 ml. of tryptose phosphate or beef infusion broth. In 77 of 82 cases of bacterial endocarditis the first positive blood culture was obtained within the first five cultures taken. Fifty-two of these cases were diagnosed by the first blood culture that was drawn. In no instance were more than 10 cultures necessary to make the diagnosis. Forty-one per cent of all of the cultures that were made were positive.

Immunization of Children by the Feeding of Living Attenuated Type I and Type II Poliomyelitis Virus and the Intramuscular Injection of Immune Serum Globulin.—Two attenuated strains of poliomyelitis virus were used in the present clinical trial, the TN^4 representing Type II and the SM^6 strain representing Type I. The viruses were given by the oral route either mixed with 10 to 20 ml. of milk or as a capsule. Patients receiving the material were children on whom antibody levels had been determined prior to the administration of the viruses. These 20 children ranged in age from 6 to 12 years and were found to lack antibodies to the types of viruses being administered.

No child developed any clinical signs of illness. The Type I (SM) virus was excreted by every child; the Type II (TN) strain was rarely excreted in the stool. All children who

ingested the Type I (SM) virus in capsule form developed the same level of antibodies as those fed the virus in milk. It was apparent that the administration of human immune serum globulin at the time that the virus was fed had no effect on antibody response.

Spinal Fluid Alcohol in Yeast Meningitis.—The authors studied five cases of cryptococcal meningitis and measured the occurrence of ethyl alcohol in the spinal fluid, which presumably is an end-product of cryptococcal metabolism of glucose. Three of these cases had abnormally low spinal fluid sugars and all three gave strong positive tests for ethyl alcohol. The remaining two spinal fluids had sugar levels within the normal range, with negative or equivocal tests for ethyl alcohol.

The authors believe that this method may be useful in distinguishing between yeast meningitis and bacterial meningitis, since control samples taken from proven bacterial meningitis were negative even though the spinal fluid sugar levels were low.

Clinical Observations on 712 Cases of Tetanus Subject to Four Different Methods of Treatment: 18.2% Mortality Rate Under a New Method of Treatment.—An extensive experience with tetanus is reported in this comprehensive paper. Six hundred ninety-two cases were admitted to one hospital over a 10-year period (1944 through 1954). The over-all mortality rate with use of sedation and antitetanus serum was 27.2%. With an improved form of management which includes the use of Mephenesin with supplementary barbiturate or chloral hydrate sedation, antibiotics, intravenous alimentation, and small doses of antitoxin (100,000 I. U.), mortality rate was reduced to 18.2% in the last 236 consecutive cases. The authors place great emphasis on the importance of specially trained nurses and a "team" approach to the management of tetanus.

Acute Meningococcemia with Vascular Collapse: An Analysis of 10 Recently Treated Cases.—Ten young adults with acute meningococcemia and vascular collapse are reported. The mortality rate was 50% in the face of treatment with antibiotics, sulfonamides, and adrenal cortical replacement therapy together with the use of arterenol.

Three of the fatalities occurred in less than 24 hours after starting treatment, and each of these showed massive adrenal hemorrhage and extensive vascular damage. An additional fatality occurred 48 hours after admission with acute myocarditis and congestive heart failure. The fifth patient died seven days after treatment had been started and had extensive damage to the brain and the cardiovascular system, the kidneys, and the adrenals.

The five patients surviving showed prolonged convalescence, with residuals of acute myocarditis in two instances. None of the survivors showed evidence of chronic adrenal insufficiency. The authors urge the use of crystalline penicillin in aqueous solution together with sulfonamides. They also administer hydrocortisone intravenously in a dosage of 100 mg. at first followed by cortisone 50 mg. every six hours intramuscularly. They emphasize the requirement of large amounts of arterenol on occasion.

Ebstein's Disease: Description of the Heart of the First Case Diagnosed During Life.—The authors have diagnosed during life the first case of Ebstein's disease and illustrate their article with the specific angiocardiographic finding of a narrow band of nonopacification separating the right atrium and auricularized right ventricle from a diminutive functioning right ventricle which is identified as a muscular ridge at the caudal line of fusion of the three leaflets of the anomalous tricuspid valve. Ebstein's disease is an anomaly of the tricuspid valve with anomalous anatomy of the leaflets. The authors refer to their earlier article on the anatomy of this anomaly (*Am. J. M. Sc.* 222:554, 1951).

Chlorpromazine Therapy in Children at the Florida Farm Colony.—One hundred fifty-three children at the Florida Farm Colony were the subjects of this study. They fell into four broad groups, mental defectives, prepsychotics, epileptics, and spastics. All patients were treated with chlorpromazine for at least six months, and most of them, for nine months. Individual daily doses ranged between 30 and 600 mg., but most patients received 75 to 150 mg. daily. In this series of 153 patients the response was classified as excellent in 52% of the total, meaning full relief of symptoms and full response to training. An additional 25% were rated as good in response, which meant that there was relief of major symptoms and improvement in training. The remainder of the patients had only fair or poor response to medication. Emphasis was placed on the beneficial effects of the drug on agitated or excited patients, whether they were mentally defective or mentally ill. The authors felt that the agent had a wide range of application and that the over-all atmosphere of the institution was significantly improved during the course of therapy.

The Effect of Salicylates and Adrenocortical Hormones on C-Reactive Protein.—The purpose of the study was to determine whether salicylates, cortisone, and corticotropin (ACTH) supress the production of C-reactive protein. Eight adult patients with generalized carcinoma were presumed not to have acute inflammation to account for their C-reactive protein elevations. Adequate amounts of acetysalicylic acid (aspirin) or corticotropin or cortisone were administered, and the C-reactive protein did not drop significantly. The findings suggested to the authors that the site of action of these drugs in rheumatic fever was specifically on the inflammatory process and not on the production elsewhere of C-reactive protein.

Elevations of Serum Glutamic-Oxalacetic Transaminase and Urinary Coproporphyrins in Pseudohypertrophic Muscular Dystrophy.—Four children with the clinical features of pseudohypertrophic muscular dystrophy were studied. In all cases the skeletal muscle biopsy findings were compatible with muscular dystrophy, but one showed, in addition, changes suggestive of dermatomyositis. In all cases the serum glutamic-oxalacetic transaminase and the urinary coproporphyrins were elevated. In one case studied the serum iron was elevated. These findings suggested the possibility to the authors that there was an increased rate of renewal and breakdown of skeletal muscle cells.

Abnormally low endogenous creatinine clearances were observed, and these clearances did not correlate with glomerular filtration rates. The serum creatinine levels were low in three of the patients. Excessive creatinuria, as reported by others, was present.

Listeria Meningitis, a Report of Eight Cases.—The report consists of clinical and bacteriological studies on eight patients with Listeria meningitis. Three of the eight were children. The bacteriological diagnosis consists of excluding diphtheroids as a contaminant. The appearance of the colonies on blood resembles that seen with β-Streptococcus. Listeria monocytogenes can be demonstrated to be motile, if it is grown at room temperature in a semisolid medium. Virulence can be demonstrated by intraperitoneal injection in mice and conjunctival application in rabbits. A polyvalent-O Listeria antiserum was also used in identification.

All of the patients received penicillin and sulphonamide drugs, and all but one received chloramphenicol as initial therapy. Five of the eight organisms were resistant to chloramphenicol. One was sensitive only to penicillin, and one was resistant to all antibiotics for which it was tested. The mortality rate was 50%.

The Effect of Ammonium Chloride Induced Maternal Acidosis on the Human Fetus at Term: I. pH, Hemoglobin, Blood Gases.—The observation of lowered fetal blood pH in infants born of diabetic mothers stimulated this investigation of ammonium chloride acidosis. The maternal acidosis produced was comparable to that observed in nonpregnant women. When the acidosis was produced at term, the fetuses exhibited a reduced pH and increased pCO_2 and reduced oxygen saturations as measured in the umbilical blood. In some cases, these changes in the newborn are as severe as those previously described with fetal apnea neonatorum following dystocia. All of the infants, nevertheless, did well clinically in the neonatal period. The data suggest a time lag in the initial adjustment of the fetus to maternal acidosis and overshooting of the adjustment during maternal recovery.

The pertinent literature is carefully reviewed.

Hyperheparinemia: Report of a Case.—Hyperheparinemia as the cause of a bleeding state is rare, but it is a distinct clinical entity and may perhaps be congenital. The patient was a 22-year-old woman who was first noticed to have excessive bleeding at the age of 3. Severe and prolonged postpartum hemorrhage led to the studies which are reported. The clotting and bleeding time were prolonged, but the tourniquet test and prothrombin time were normal. The most significant laboratory test was the thrombin time, which is determined by the addition of thrombin to the patient's blood. With the addition of thrombin, the clotting time is proportional to the concentration of heparin. To verify that a prolonged thrombin time is due specifically to heparin, the determination is repeated, after addition of either protamine sulfate or toluidine blue. If the thrombin time becomes normal after this addition, the presence of heparin is established. The most satisfactory therapeutic results were obtained with the combined use of cortisone and the transfusion of fresh frozen plasma. The use of toluidine blue and protamine sulfate in the patient was unsuccessful.

The authors cite a case report by Heni and Krauss in which a father and daughter had a similar condition. The possibility that such a condition may be hereditary is further suggested by an observation that a mink from a highly inbred stock developed a bleeding state due to hyperheparinemia.

The Production of Antibody by Splenectomized Persons.—Seven adult splenectomized patients who had been previously actively immunized against tetanus were given a booster dose of tetanus toxoid, and their antibody response was measured at weekly intervals thereafter. The amounts of tetanus antitoxin in the serums were determined by titration in mice performed by intramuscular injections of appropriate dilutions of the serum to be tested mixed with standardized doses of tetanus toxin. All seven patients made considerable antitoxin, comparable in amounts to that produced by similarly immunized normal persons. Previous work relative to the findings is reviewed.

Iron Enzymes in Iron Deficiency: I. Cytochrome C.—This preliminary work was carried out to test the assumption that the symptoms of iron deficiency are due only to a decrease in the circulating hemoglobin. Rats were fed either a normal or an iron-deficient diet and were then bled at appropriate intervals. A marked decrease in the cytochrome C content of the liver and kidneys of iron-deficient rats was demonstrated in comparison to the control group. This decrease exceeded the slight decrease in hemoglobin concentration. This finding may lend some support to the concept that the symptomology of iron deficiency may be related to disturbance of tissue metabolism rather than to a mere reduction in the circulating hemoglobin.

Changes in Serum Pseudo-Cholinesterase Levels in Patients with Diseases of the Heart, Liver, or Musculoskeletal Systems.—Serum pseudocholinesterase tests were performed on a large number of patients by use of the method of Michel. In patients with myocardial infarction, a persistently falling level suggested a bad prognosis; however, it was not of much help in the routine management of the patient. The test was useful in differentiating patients with obstructive disease of the biliary tract from those with hepatocellular disease, in which condition the values were depressed. The method was somewhat more sensitive than the serum transaminase test in this regard. It was also found that the serum cholinesterase test is of value in differentiating dermatomyositis from other collagen diseases.

Electroencephalographic Correlation of Laughing Fits.—The authors document clinical and electroencephalographic observations of four patients, all children, with "laughing fits." The clinical diagnoses included papilloma of the third ventricle infiltrating into the tip of the temporal lobe; postencephalitic, mesencephalic seizures; birth trauma with mental retardation and akinetic-motor and temporal lobe seizures, and birth trauma with hyperkinetic behavior disorders and nocturnal laughing fits. They conclude that the laughing fits are epileptic in nature, because the fits were inappropriate to any environmental factors and were preceded or were a part of other epileptic phenomena, plus the fact that there were demonstrable paroxysmal electroencephalographic abnormalities.

In reviewing the available literature on the subject they state that laughing fits are prone to occur when there is a disturbance around the third ventricular area and the diencephalon with projection to the temporal lobe. They believe that their recorded observations indicate a possibility of limbic area activation as being responsible for epileptic laughing fits.

Clinical and Microbiological Aspects of Salmonellosis.—Seventy-five patients comprised the study group; forty of these were adults, and thirty-five were infants and children ranging in age from the newborn period to 12 years of age. In the latter group the average age of the patients was 1.7 years, the youngest being 3 days old and the oldest, 11 years. Twenty-six of this group were one year old or less, with ten of them having been prematurely born. The infections occurred among the prematurely born infants at widely separate times during the period encompassed by this survey and do not represent a single outbreak of this disease in a nursery. Males comprised 46% of the group, and 86.5% were Negroes.

The commonest prominent signs and symptoms in both adult and pediatric patients were fever and diarrhea. Diarrhea was conspicuously commoner in the pediatric age group than in the adults (twice as often). Other prominent signs and symptoms in the children were vomiting, dehydration, abdominal distention, cough, malaise, and abdominal cramps. In the opinion of the authors, there were only four instances in which death was attributable directly

to salmonellosis. Three of these were adults and one was a child. Nevertheless, the total mortality rate for the entire group of patients was 20%. Shedding of salmonellae in stools following apparent clinical cure was variable, but the interval ranged from 10 to 604 days, with an average of 127 days. The strains isolated and tested for in vitro antibiotic susceptibility showed them to be uniformly sensitive to chloramphenicol. One-half of the strains were also susceptible to the tetracyclines; streptomycin was ineffective. The authors believe that in spite of the superiority of chloramphenicol its clinical use either alone or concomitantly with other agents seemed to exert little if any influence on the fatality rate.

The Effect of Meprobamate (Equanil) on Brain-Damaged Patients.—In this study 105 patients with brain damage demonstrable by the presence of abnormal electroencephalographic tracings were given meprobamate in a dosage adjusted to the individual needs of each patient and based on a clinical appraisal of the severity of symptoms. In 12 instances the drug was administered four times daily; the remaining patients received it three times daily. The predominant daily dose was 1200 mg., ranging from 400 mg. to 3600 mg. Evaluation of responses was based on clinical judgment. In the opinion of the authors, meprobamate is a neuropsychiatric drug of high merit in the treatment of patients with organic lesions of the brain and was the drug of choice in selected patients. No other drug was given during the study, and more than 80% of the spastic and 97% of the athetoid patients responded with at least moderate remission of their neuromuscular symptoms. Behavioral problems almost vanished in 50% of the cases and were moderately relieved in 97%. Improvement was maintained over a two-year period while medication continued at dosages as high as 3600 mg. daily. Some patients improved sufficiently to benefit from physiotherapy or psychotherapy for the first time. Eleven patients had side-effects of drowsiness.

American Journal of Medicine, New York

Abstracted by Hugo Dunlap Smith, M.D.

23, No. 6 (Dec.) 1957

Drug Reactions Characterized by Cholestasis Associated with Intrahepatic Biliary Tract Obstruction. A. B. Gutman.—p. 841.

* Splenic Venography and Intrasplenic Pressure Measurement in the Clinical Investigation of the Portal Venous System. M. D. Turner, Sheila Sherlock, and R. E. Steiner.—p. 846.

Allergy to Chlorpromazine Manifested by Jaundice. Leo E. Hollister.—p. 870.

The Agammaglobulinemias: Relations and Implications. Casimir A. Domz and Delbert R. Dickson.—p. 917.

Paraldehyde Intoxication with Metabolic Acidosis: Report of Two Cases, Experimental Data and a Critical Review of the Literature. James N. Hayward and Buris R. Boshell.—p. 965.

Renal Tubular Acidosis with Organic Aciduria During Paraldehyde Ingestion: Six Year Study of an Unusual Case. J. R. Elkinton, E. J. Huth, J. K. Clark, E. S. Barker, and D. Seligson.—p. 977.

Metabolic Acidosis Occurring During Administration of Paraldehyde. Christine Waterhouse and Edward A. Stern.—p. 987.

Splenic Venography and Intrasplenic Pressure Measurement in the Clinical Investigation of the Portal Venous System.—Turner, Sherlock, and Steiner report on 126 splenic venograms and intrasplenic pressure measurements in 109 adult and child patients. Complications were infrequent when the following contraindications were observed: the presence of superficial an injection—most of the dye went into the peritoneum, causing brief pain, and jaundice, an abnormal platelet count, or an abnormal prothrombin time. Only four had obvious hemorrhage, and these all recovered following transfusions; three with portal cirrhosis and esophageal varices had hematemesis within 36 hours of the procedure; in six, owing to too in one the dye was injected into the colon, but without any untoward reaction. Failure of the procedure occurred 14 times, usually due to breakdown in the x-ray apparatus. To balance these drawbacks, the procedure was of great value in investigating the source of gastrointestinal bleeding; in evaluating the possibility, and postoperatively, the effectiveness of portacaval shunts; in differentiating cirrhosis from extrahepatic portal vein obstruction as a cause for splenomegaly, and in ascertaining whether neuropsychiatric symptoms in patients with cirrhosis were due to cerebral nitrogenous intoxication, secondary to spontaneous portacaval shunts. Less commonly the procedure was used to study suspected hepatic tumors and cases of unexplained ascites. It was stressed that large splenic veins can be seen without portal hypertension in Gaucher's disease and in cases of portal vein obstruction in which large collaterals have decompressed the portal vein. Although, on the whole, intrasplenic pressure correlated with a tendency to gastrointestinal hemorrhage, bleeding from varices did occur with normal portal pressure—a fact that would indicate that reflux and ulceration may play a role.

American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig Jr., M.D.

77, No. 5 (May) 1958

Comparative Evaluation of Epinephrine and Aminophylline as Bronchodilator Agents. Ross C. Kory, Robert A. Pribek, and Richard O. Sternlieb.—p. 729.
The Induction of Respiratory Acidosis by Oxygen Breathing. Herman F. Froeb, Charles I. Leftwich, and Hurley L. Motley.—p. 737.
Histoplasmosis: A Review of One Hundred Consecutive Hospitalized Patients. Francis J. Curry and James A. Wier.—p. 749.
* The Disc-Method Tuberculin Test. Sol Roy Rosenthal.—p. 778.
The Effects of Extended Incubation on Propagability of Tubercle Bacilli. H. E. Kennedy, H. M. Vandiviere, and H. S. Willis.—p. 802.
The Effect of Chemotherapy on the Leukocytic Sensitivity to Tuberculin in Guinea Pigs Experimentally Infected with Mycobacterium Tuberculosis H37 Rv. H. E. Hall and M. Scherago.—p. 815.
Pyrazinamide-Induced Acute Yellow Atrophy of the Liver: Case Report and Post-Mortem Findings. Theodore N. Spengos and Rod Cuizon.—p. 858.
Application of Hooke's Law to the Elastic Properties of the Lung. Robert Gilbert et al.—p. 863.
Short-Term Therapy in Experimental Tuberculosis. Florence K. Fitzpatrick.—p. 867.

The Disc-Method Tuberculin Test.—The disc method for tuberculin testing, a modification of the Heaf test, is introduced by the author. The method of testing, description and interpretation of reactions, and care of the apparatus are discussed. The author concludes that the degree of sensitivity of the test lies somewhere between 1:1000 (10 TU) and 1:100 (100 TU) Old Tuberculin, as determined by the Mantoux method. Advantages listed for the test are: (1) that it is relatively painless and (2) easy to perform and easy to interpret; (3) reading is simplified; (4) no dilutions of tuberculin are necessary, and (5) elimination of needle and syringe.

Comment: While an accurate test dose of tuberculin solution is always highly desirable, it must be admitted that lack of cooperation often poses a problem when the Mantoux test is used in infants and young children. If degree and interpretation of reaction can be satisfactorily standardized, the disc-method tuberculin test may be of particular value when employed in the testing of large groups of infants and/or young children.

Circulation, New York

Abstracted by Anthony C. Nolke, M.D.

17, No. 4, Pt. 1 (April) 1958

Muscular Dystrophy: Catheterization Studies Indicating Latent Congestive Heart Failure. S. Gailani, T. S. Danowski, and D. S. Fisher.—p. 583.
Clinical Progress—Systolic Murmurs. Aubrey Leatham.—p. 601.

17, No. 5 (May) 1958

The Lewis A. Conner Memorial Lecture: Rheumatic Heart Disease—A Challenge. Charles A. Rammelkamp Jr.—p. 842.

Journal of Pediatrics, St. Louis

Abstracted by Demetrius G. Traggis, M.D.

52, No. 1 (Jan.) 1958

Blood Pressure Studies in Infants and Children with an Electric Microphone. R. K. Endres, D. Goldring, and M. R. Behrer.—p. 1.
An Analgesic Mixture for Minor Surgical Procedures in Young Children. F. N. Mitchell and G. R. Minor.—p. 16.
The Incidence of Allergic Disease in the General Practice of Pediatrics. W. G. Crook, W. W. Harrison, and S. E. Crawford.—p. 20.
Lysine Tolerance in Infants. E. Dubow, A. Maher, D. Gish, and V. Erk.—p. 30.
The Antibody (Hemagglutinin) Response as a Tool for Etiologic Diagnosis of Diarrheal Disease. E. Neter and L. Suskind.—p. 38.
The A-B-O Blood Groups in Relation to Prematurity and Stillbirth. S. A. Plotkin.—p. 42.
Observations on the Plasma Lipoproteins in a Case of Tay-Sachs Disease. H. W. Dargeon, M. Barclay, D. N. Calathes, and M. J. Brownell.—p. 48.
* Addison's Disease in Children. R. E. Greenberg.—p. 54.
Sucrosuria in Association with Mental Deficiency and Hiatal Hernia. G. G. Woodruff.—p. 66.
Megimide in the Treatment of Severe Barbiturate Poisoning. B. E. Nolan.—p. 73.
Malathion Poisoning in a 34-Month-Old Child Following Accidental Ingestion. H. Goldman and M. Teitel.—p. 76.

The Relation of Pectus Excavatum to Pectus Carinatum. C. W. Lester.—p. 82.
An Objective Survey of Dental Malocclusions in Children. B. S. Dunham.—p. 87.
Speech Problems in Children. I. Lehrhoff.—p. 91.
Clinical Pathological Conference, the Children's Medical Center, Boston, Mass.—p. 96.
Recent Approaches to the Biology of Schizophrenia.—p. 103.
Poliomyelitis-like Illnesses.—p. 111.

52, No. 2 (Feb.) 1958

Familial Goiter with Defect in Intrinsic Metabolism of Thyroxine Without Hypothyroidism. G. W. Clayton, J. D. Smith, and A. Leiser.—p. 129.
A Study of Pathology of Stillbirths and Neonatal Deaths in South India. G. G. Hadley, E. W. Gault, and M. D. Graham.—p. 139.
The Neck-Righting Reflex in Children. R. L. Spitzer, Y. Kramer, and R. Rabkin.—p. 149.
Acne: A New Approach to an Old Problem. J. W. Baird.—p. 152.
Marchesani Syndrome. J. Zabriskie and M. Reisman.—p. 158.
Sickle Cell Disease with Salmonella Osteomyelitis. A. R. Roberts and L. E. Hilburg.—p. 170.
Acute Leukemia and Mongolism. W. W. Sutow and V. C. Welsh.—p. 176.
Gargoylism (Hurler's Syndrome; Lipochondrodystrophy; Dysostosis Multiplex). R. P. Epps and R. B. Scott.—p. 182.
Coarctation of the Abdominal Aorta. F. S. Gerbasi, R. S. Kibler, and A. M. Margileth.—p. 191.
Symptomatic Patent Ductus Arteriosus in Infancy. J. A. Little and R. Sunico.—p. 199.
Unilateral Renal Vein Thrombosis in an Infant with Sepsis Due to Salmonella Choleraesuis: Nephrectomy with Recovery. J. A. de la Torre, E. Villalpando, H. Esparza, and J. Olarte.—p. 206.
* Giant Hemangioendothelioma with Associated Thrombocytopenia. R. G. Scherz, J. M. Lauro, and L. J. Gepert.—p. 212.
Clinical Pathological Conference, the Children's Medical Center, Boston, Mass.—p. 217.
Reflections on Infantile Gastroenteritis and Its Treatment. S. Levin.—p. 227.
Aseptic Meningitis Due to Strains of Echo Virus.—p. 245.

Addison's Disease in Children.—The author reports on two cases of apparent primary adrenal atrophy. Up to 1946 Jaudon found 59 patients with Addison's disease under 15 years of age (12 under 10 years). Fifty-three of these cases were due to tuberculosis. In 1952 Talbot et al. reported nine cases, in five of which no cause could be found. The two cases reported here were not clear-cut for some time.

The first case, a boy, was first seen at about age 11 years. Twelve months previously (after a sore throat) he developed dehydration and disorientation; six months previously, the same type of episode after tonsillectomy and adenoidectomy; during that year he developed increasing lethargy, irritability, fatigability, and diminished school performance; physical examination revealed height and weight below the 3d percentile; scattered nevi and diffuse tan pigmentation (not in mucosa, nipples, or hands); bone age four years behind chronological age; serum electrolytes normal (K, a high normal); PBI normal; insulin tolerance test showed insulin sensitivity; circulating eosinophils, 66 per cubic centimeter. The child was first treated for several months with methyl testosterone, with no results. Six months later there was another episode of dehydration and semicoma. History of excessive salt intake. K 6.5, Na 137, Cl 78, CO_2 18, BUN elevated. The patient was treated with aqueous adrenal extract, hydrocortisone, and cortisone acetate and fluids, with rapid response. No cause for the insufficiency could be found. Injections of corticotropin gave no change in circulating eosinophils nor in urinary 17-ketosteroids, demonstrating the inability of the adrenals to respond to pituitary stimulation. He was put on cortisone acetate, 5.75 mg. twice a day orally, and 0.15 mg. of fludrocortisone a day. Since then growth has occurred and symptoms have disappeared.

The second case was a 7½-year-old white boy who since the age of 3 years, had had several episodes of fever, dehydration, delirium, and also convulsions. The only previous findings were diffuse pigmentation, low blood sugar, and K between 5 and 6 mEq. per liter. Other electrolytes were normal, but blood was drawn at a time of dehydration. At time of diagnosis pigmentation included oral mucosa. Cl was 88 mEq. per liter; BUN, 26 mg. %; rest, normal. Studies for any disease as cause of adrenal insufficiency were negative. Insulin-tolerance test denoted increased sensitivity. Robinson-Power-Kepler water test was normal. Eighty units of corticotropin daily for eight days gave no significant response with respect to urinary 17-ketosteroids and 17-hydroxycorticoids. Plasma 17-hydroxycorticoids were not demonstrated before and four hours after corticotropin gel (80 units). The child was treated with 12 mg. of cortisone acetate twice a day and 0.1 mg. of fludrocortisone, with good results.

The author points out the difficulties in making the diagnosis in his two cases and related them to the probable slowly developing adrenal atrophy. The author emphasizes the importance of considering this syndrome in any child with asthenia, anorexia, poor weight gain,

recurrent dehydration, and/or hypoglycemia and general debility. He also points out the importance of obtaining a history of excessive salt intake.

The author discusses the well-known tests used in the diagnosis of adrenal insufficiency, such as glucose-tolerance, insulin-sensitivity, and electrolyte disturbance (which may be masked by a reduction of extracellular volume). In his experience, a K level seemed consistently a little high regardless of the other electrolytes. The most significant tests, he feels, are the plasma 17-hydroxycorticoids. Normally these should rise at least 100%. Prolonged corticotropin administration (over three days) and adequate dosage should be used.

In the management of this condition, he feels that correction of dehydration and electrolytes, correction of hypoglycemia, treatment of precipitating cause, and replacement of hormones are the chief factors. He prefers to use aqueous adrenal cortical extract along with hydrocortisone. Desoxycorticosterone acetate is used mainly when hyperkalemia is present. For the maintenance of these patients, he points out the advantage of small doses of 7*a*-fluorohydrocortisone (the fluorine iron greatly increases the salt-retaining properties).

Giant Hemangioendothelioma with Associated Thrombocytopenia.—The authors report the case of a child with the syndrome of giant hemangioendothelioma with associated thrombocytopenia. At the age of one year a large ecchymotic area was noted on the anterior chest wall. Chest x-ray suggested fluid. Thoracentesis yielded grossly bloody fluid. Changes in the ribs, decalcification, coarse trabeculations, and periosteal thickening were noted. Bone marrow and CBC, including platelets, were normal. Biopsy of the area revealed hemangioendothelioma. About two months after onset, an increase in size of the tumor was noted, accompanied by ecchymotic areas elsewhere and moderate respiratory distress. Platelets were 8000; Hb., 9 gm.; bone marrow revealed increased lymphocytes, some reduction in erythroid cells, and increased, but normal-appearing, megakaryocytes. The patient was started on prednisone, 10 mg. a day. Thirteen days later, x-ray therapy (total dose of 2000 r) was started; six days after this platelets were 610,000 and prednisone was discontinued. Platelets again dropped, and prednisone, 15 mg. a day, was reinstituted. Six days later platelets were 130,000 and x-ray was restarted. Ninety days later the tumor had regressed greatly. Prednisone was gradually decreased and stopped two and one-half months later. She has been well since.

The authors reviewed the 14 cases in the literature of the same syndrome. Characteristics common to all are (1) a large vascular tumor involving a large area, (2) thrombocytopenia, (3) clinical evidence of hemorrhage into the tumor with evidence of ecchymoses and petechiae elsewhere, and (4) often anemia secondary to hemorrhage in the tissues. In commenting on the cases in the literature they noted that management has included radiation therapy, splenectomy, and, in one case, steroid therapy. They pointed out the inadequacy of the dosage in the one case treated with cortisone and the questionable benefit of splenectomy in the one case in which it was said to have been beneficial (it had been treated with radiation, and the lesion had become infected). They also agreed with Dr. Good as to the cause of the thrombocytopenia in this syndrome, namely, segmentation of platelets. The authors feel that in their case prednisone was of very definite value in causing a rise of platelets.

Comment: There seems to be general agreement as to the fact that the thrombocytopenia clears up when the hemangioma regresses. However, with the small number of cases reported, there does not seem to be any convincing proof that the methods of treatment used—irradiation, steroids, splenectomy—have had any real effect in hastening the regression of the hemangioma. As mentioned by the authors, the one case of apparent benefit by splenectomy had been treated with radiation and had also become infected. When one looks over the cases treated by irradiation, one finds that often several months of treatment were necessary before the tumor regressed. As shown by many authors, these tumors have a natural tendency to spontaneous regression, and one wonders whether or not in some of these cases this was actually what happened. Furthermore, changes in the tumors secondary to infection may have been responsible for the regression of some. In the author's case it appears that prednisone may have been helpful; yet they, too, had used radiation and the child was 15 months old at the time of regression of the tumor. We are, at present, following an infant with this syndrome. Twenty milligrams of prednisone a day has made no change in the platelet count. There was some diminution in the numbers of ecchymoses and petechiae coincidental with the administration of prednisone, which may have been due to a nonspecific effect on the capillaries. How-

ever, one case is not sufficient to say. The severity of the disease in many of these infants warrants the use of radiation and/or steroids. At present there does not seem to be enough statistical evidence to prove that they are of real value.

Maandschrift voor kindergeneeskunde, Leiden, Netherlands

Abstracted by S. van Creveld, M.D.

26, No. 1 (Jan.) 1958

Pediatric Odontology I. R. W. Broekman.—p. 2.
* Hemorrhagic Symptoms in Leukemia. S. van Creveld.—p. 10.
Occurrence of an Accessory Atrioventricular Muscular Fiber in a Baby with Paroxysmal Tachycardia and the Wolff-Parkinson-White Syndrome. V. H. de Villeneuve and H. E. Schornagel.—p. 23.

26, No. 2 (Feb.) 1958

Pediatric Odontology II. R. W. Broekman.—p. 37.
Ideas on the Prevention of Accidents in Childhood. H. H. van Gelderen.—p. 47.
Recurrent Asthmatiform Dyspnea in a Baby. D. de Vliger.—p. 54.
Combination of Arachnodactyly, Microcephaly and Thrombocytopenia in a Baby. J. H. W. Pielage.—p. 59.

26, No. 3 (March) 1958

Pediatric Odontology III. R. W. Broekman.—p. 73.
* Congenital Malformations with Agenesis of the Spleen. P. Arons.—p. 80.
Cor Triatriatum. A. Vermeersch, K. K. Bossina, and G. K. van der Hem.—p. 90.

26, No. 4 (April) 1958

Bacteriology of Otitis Media in Children. A. C. W. Derks, R. Voorhorst, and H. A. E. van Dishoeck.
Congenital Adrenogenital Syndrome of the Salt-Losing Type (Syndrome of Debré-Fibiger)—Familiar Case: Effect of Long-Continued Cortisone Therapy on the Somatic Development; Experiences After 5 years. F. de Muelemeester and W. A. M. Weyers.

Hemorrhagic Symptoms in Leukemia.—Discussion is presented of the various causes of hemorrhages in acute leukemia and of the therapeutic means available to control such hemorrhages. The use of fresh siliconized blood and of fresh plasma is stressed, and the role of platelets is extensively discussed.

Congenital Malformations with Agenesis of the Spleen.—The syndrome of congenital abnormalities of heart and great vessels, associated with agenesis of the spleen and other malformations, is discussed in detail. A case report is given as illustration.

Especially mentioned are the abnormalities in the morphology of the blood and the increased tendency to severe infections found in this syndrome. The latter is brought in relation to the severe infections also often found after splenectomy in young children.

Medical Journal of Australia, Sydney

Abstracted by George H. Lowrey, M.D.

2, No. 24 (Dec. 14) 1957

A Case of Infantile Glaucoma Associated with Maternal Rubella. Kevin O'Day.—p. 861.

2, No. 26 (Dec. 28) 1957

Some Observations on Certain Head Injuries of Infants and Children. M. Sofer Schreiber.—p. 930.
Immunization by the Blood Antigen Kidd (JK^a) in Pregnancy and in Blood Transfusion. R. T. Simmons, J. J. Graydon, Rachel Jakobowicz, J. Santamaria, and Margaret Garson.—p. 933.

1, No. 1 (Jan. 4) 1958

Illness in Twins: V. Observations on Social Development. F. Pitman.—p. 6.

1, No. 2 (Jan. 11) 1958

Preparation of Children for Tonsillectomy. H. Julie Jones.—p. 32.
Exchange Transfusion in Hepatic Coma: Report of a Case. Charles Lee and Arnold Tink.—p. 40.
A Case of Acute Poisoning by Benzene Hexachloride. R. W. Nicholls.—p. 42.

1, No. 3 (Jan. 18) 1958

* Subdural Hygroma. J. Bryant Curtis.—p. 69.
Atopic Dermatitis (Generalized Neurodermatitis): The Atopic Dermatitis-Asthma-Hay Fever Syndrome. Emil Milder.—p. 72.

1, No. 4 (Jan. 25) 1958

Infective Hepatitis: Its Incidence and its Sequelae. C. E. Marshall.—p. 93.
Infectious Hepatitis: Report of an Outbreak, Apparently Water-Borne. Edgar C. Wallace.—p. 101.
Recurrent Pyuria in Children. L. D. Wheeler.—p. 106.
* Recurrent Pyuria. A. R. Tink.—p. 107.
Perforation of Meckel's Diverticulum by Grape Seeds. A. Rumore.—p. 110.

1, No. 5 (Feb. 1) 1958

Some Statistical Observations on Fluoridation Trials. Philip R. N. Sutton and Arthur B. P. Aimes.—p. 139.
A Review of 182 Cases of Tetanus. Ruth Molphy.—p. 141.

1, No. 6 (Feb. 8) 1958

Perineal Testicle. W. J. Sleeman.—p. 187.

1, No. 7 (Feb. 15) 1958

Footprints: The Jubilee of the Pediatric Society in Victoria. Howard Boyd Graham.—p. 201.
* Jaundice of Prematurity. Kate Campbell.—p. 206.
Changing Aspects in Pediatric Orthopedics. Douglas Galbraith.—p. 208.
"What Can We Do for the Child Who Bleeds?" John H. Colebatch.—p. 210.
Toxoplasmosis: Editorial Comment.—p. 217.

1, No. 8 (Feb. 22) 1958

* Neonatal Osteomyelitis: A Disease Different from Osteomyelitis of Older Children. A. Murray Clarke.—p. 237.
The Superficial Inguinal Pouch and the Undescended Testis. Peter Jones.—p. 239.
Testicular Infarction in Infancy: Its Association with Irreducible Inguinal Hernia. J. G. Sloman and R. E. Mylius.—p. 242.
Minor Surgical Conditions of the Anus and Perineum. F. Douglas Stephens.—p. 244.
* Meningitis in Melbourne Due to E. C. H. O. Virus: I. Clinical Aspects. J. A. Forbes.—p. 246.
* Meningitis in Melbourne Due to E. C. H. O. Virus: II. Laboratory Aspects (Preliminary Report). A. A. Ferris and F. A. Lewis.—p. 248.

Subdural Hygroma.—The author defines a subdural hygroma as a collection of clear, colorless, or yellow fluid, usually following trauma. The terms serous meningitis and subdural hygroma have also been applied, as well as subdural effusion. Seven cases are described, occurring in infants. In one case there was definite history of head injury at 5 months. In three cases there was a history of rapid or difficult labor. In two there was a history of probable infection, and in one case no relevant history was obtained. In one child a hemiparesis on the same side of the lesion was present. In none of the babies operated on was a membrane found as described by Ingraham and Matson. All the patients reported here were treated by multiple subdural taps. The results were good in all but one case, this patient dying.

Recurrent Pyuria.—The frequent absence of signs of urinary tract infection in infants is pointed out. The author makes the statement that urinary tract infection in the newborn boy is as frequent as in the girl. Findings such as irritability, failure to thrive, and unexplained dehydration should make one suspect chronic or recurrent urinary tract infection. Fever and evidence of urinary tract irritation may be absent particularly in small children or infants. Of the causes, one of the commonest is the finding of congenital valves of the posterior part of the urethra. The author objects to the frequency with which instrumental dilatation of the urethra is carried out in girls with cystitis. Recurrence is believed to be due often to suboptimal therapy, and avoidance of failures will be realized if the proper drug is used for an adequate period of time.

Jaundice of Prematurity.—The author feels that the following conditions favor the development of kernicterus in the presence of jaundice: hypoxemia, excessive blood from the placenta, trauma to vascular areas, particularly the face and scalp, dehydration, excessive vitamin K administration, infection, and twin births. "It would appear that the important factor affecting the vulnerability of the neuron is its state of oxygenation." The clinical signs of a baby in danger of kernicterus are enumerated as follows: (1) loss of vigor with decrease of activity, (2) loss of appetite, (3) vomiting of recently ingested formula that later becomes bile-tinged. The author states that in the presence of all of these symptoms an exchange transfusion is performed. If some symptoms are present but not all, and the serum bilirubin content is over 18 mg. %, an exchange transfusion is indicated. Of 390 babies so treated, 2 infants died of complicated kernicterus. No baby died of kernicterus that was not complicated by some such condition as pneumonia.

Neonatal Osteomyelitis: A Disease Different from Osteomyelitis of Older Children.—An analyses is made of 24 cases seen at the Royal Children's Hospital, Melbourne, Australia, during the past five years. The author stresses the differences between the disease seen at this age and at a later age. The bones involved were femur, 8 cases; maxilla, 6; humerus, 5, and vertebra, 3. Other bones were involved, but these were the commonest. Only three patients of this series had involvement of the upper end of the femur, in contrast to the common adult lesion. In the case of vertebra involvement the primary sign of infection was not discovered until large retroperitoneal abscesses had developed. Prompt diagnosis is difficult because the symptoms are often nonspecific. The author lists the commonest as follows: malaise, poor color, failure to gain weight, fever, diarrhea, tenderness especially on motion, localized swelling, conjunctivitis, perinasal discharge, and abdominal mass. There is often little or no toxemia; fever is often absent, and the patient may take feedings well. Abscess formation and joint involvement are common. The author states that, since the diagnosis is frequently delayed, radiological signs were present in all cases. In nearly all of the cases reported, Staphylococcus aureus was grown from aspirated material. All organisms were resistant to penicillin. In the cases where the maxilla was involved the diagnosis was not made before pus was exuding from sinuses inside the mouth. The first sign is often swelling of the cheek, particularly the infra-orbital area or eyelid. Treatment is briefly discussed, with emphasis on the fact that good results will not occur until early diagnosis is made.

Meningitis in Melbourne Due to E. C. H. O. Virus: Part I. Clinical Aspects; Part II. Laboratory Aspects (Preliminary Report).—Prior to 1956 the number of patients with virus meningitis or menigoencephalitis without paralysis generally paralleled the incidence of paralytic poliomyelitis. In August, 1956, the number of cases of paralytic poliomyelitis fell, whereas the cases of virus meningitis without paralysis increased. During the following six months only 9 patients with poliomyelitis were admitted to the hospital, in contrast to 138 patients with virus meningitis. The disease was characterized by a duration of four or five days with malaise, headache, fever, nausea, vomiting, muscle pains, sore throat, and eventually stiffness of the neck and back. The cerebrospinal fluid usually contained between 20 and 500 leukocytes per cubic millimeter. The cells were both polymorphs and lymphocytes, with the former predominating early in the disease. Protein level is increased, and the sugar concentration is normal. In the epidemic described the age most commonly affected was between 6 and 10 years, with a less-marked peak between 26 and 30 years. Of 217 patients studied, 57% yielded ECHO viruses from stool specimens and 7 of 36 cerebrospinal fluid specimens yielded the same virus. The authors state that they were unable to type these viruses against Strains 1 to 14. The results with higher types were not reported.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

53, No. 20 (May 16) 1958

This number reports the meeting of the German Society for Internal Medicine giving some reviews.
Etiology, Pathogenesis, and Prophylaxis of Human Malformations. K. Idelberger.—p. 859.
Causes and Sequelae of Genetically Conditioned Disturbances. K. H. Degenhardt.—p. 862.
Malformations of the Upper Urinary Tract and Their Consequences. H. K. Bünber.—p. 867.

53, No. 21 (May 23) 1958

* Hereditary Nystagmus and a Special Benign Form of Congenital Nystagmus. H. Kirchmair.—p. 928.
Treatment of Rheumatic Diseases in Childhood. U. Köttgen and E. Christmann.—p. 940.

53, No. 22 (May 30) 1958

Surgery of the Open Heart in Hypothermia and with the Use of an Artificial Heart-Lung System. E. S. Bircherl.—p. 985.

Hereditary Nystagmus and a Special Benign Form of Congenital Nystagmus.—The different forms of hereditary nystagmus are discussed shortly. Four cases are reported, seen in Arab boys. In a boy 7 years of age the nystagmus gradually disappeared from the age of 3 years. In another, 6 years of age, the nystagmus could hardly be seen any longer. These four boys had congenital familial nystagmus with normal vision without other symptoms. The nystagmus disappeared entirely or nearly entirely during early childhood, and the name "benign congenital nystagmus" is proposed.

Monatsschrift für Kinderheilkunde, Berlin

Abstracted by Hans Hartenstein, M.D.

105, No. 11 (Nov.) 1957

Allergy, an Immuno-Biological Problem. Hans Schmid.—p. 401.
Allergy in Childhood. Gerhard Joppich.—p. 406.
About the Necessity of Using Special Care in the Use of Centrally-Acting Spasmolytic Agents in the Treatment of "Spastic Pylorus-Syndrome." Hans-Rudolf Wiedemann and Leonore Middendorf.—p. 411.
Unipolar Chest Leads in the Electrocardiogram of Premature Infants with Special Emphasis on the Vector Relationships. Joachim Stoermer.—p. 414.
Acute Mercury Poisoning in Infancy. Kurt Lorenz.—p. 417.
Hereditary Factors in the Development of the Osseous System. Albert Breitbach.—p. 421.
Education or "Breaking-In"? (Crises During Puberty). Horst Hartmann and Max Heinrich.—p. 423.
Case Reports: Fuso-Spirochetal Disease (Vincent) of the Rectum in a 12-Year Old. Liebgart Reinhold and Sabine Wagner.—427.
Review Article: Endocrinology. Kurt Nitsch.—p. 434.

105, No. 12 (Dec.) 1957

Use of the Schellong Test of Activity in Children with Rheumatic Fever. Gert Koelle.—p. 441.
* Carry-Over of Maternal Antibodies in Infants with Erythroblastosis. D. H. Gallasch.—p. 445.
Citric Acid in Acidified Milk Feedings. Georg O. Harnapp.—p. 448.
State of and Nutritional Value of Proteins in Raw and in Briefly Boiled Human Breast Milk. Helmut Karte.—p. 451.
International Poliomyelitis Conference in Geneva, July, 1957.—p. 461.
Review Article: Blood and Blood-Forming Organs. Klaus Seelemann.—p. 464.

Carry-Over of Maternal Antibodies in Infants with Erythroblastosis.—Maternal antibodies were detected until the 104th day of life in the blood of an infant treated with repeated small transfusions because of erythroblastosis fetalis due to Rh incompatibility. Half-life of the antibody was about 30 days. During the aregenerative phase of the bone marrow, which lasted for almost 7 weeks, from the 10th day of life on, antibody titer remained unchanged. Further decrease of antibody can be explained by absorption of the Rh-positive red blood cells which were being destroyed. Only after complete disappearance of antibodies, by the 119th day of life, could the infant's own Rh-positive red cells be discovered, which continued to increase in number, as determined by differential agglutination.

Nederlandsch tijdschrift voor geneeskunde, Haarlem, Netherlands

Abstracted by S. van Creveld, M.D.

102, No. 1 (Jan. 4) 1958

* Mongolism, a Genetic Problem? A. van Straaten.—p. 8.

102, No. 3 (Jan. 18) 1958

* Dystrophia Bullosa Hereditaria, Typus Maculatus. M. J. Woerdeman.—p. 111.

102, No. 4 (Jan. 25) 1958

* Developmental Dyslexia (Reading Disorders). F. Grewel.—p. 183.

102, No. 14 (April 5) 1958

* Chronic Myocarditis. S. van Creveld and H. A. P. Hartog.
* Hyaline Membranes in the Lungs of Newborns. W. H. Brummelkamp.

102, No. 15 (April 12) 1958

Treatment of Acute Intussusception in Children. A. M. H. Vogelenzang.—p. 710.
A Case of Congenital Idiopathic Hypoprothrombinemia. K. S. Radhakishun, S. A. ten Bokkel Huinink, and H. J. Vermeulen.—p. 712.

102, No. 16 (April 19) 1958

* Generalized Arteriosclerosis in Infants. P. J. A. Ruys and V. Seynhave.

102, No. 17 (April 26) 1958

A Rare Case of Hemorrhagic Diathesis, Caused by Deficiency of Plasma Thromboplastin Antecedent (PTA). M. Wijffels and L. Walpot.

102, No. 19 (May 10) 1958

* Cardiovascular Deviations in Arachnodactyly. F. S. P. van Buchem.—p. 893.
* Syndrome of Albright. J. D. Schendstok and A. J. Develing.—p. 913.

Mongolism, a Genetic Problem?—A comparative study of twins has indicated the hereditary character of the condition, as well as the presence of a positive correlation to the mother's advanced age. The genetic and cytoplasmatic factors responsible are discussed. Mongolian idiocy is probably an irregularly dominant hereditary character, with slight familial expression. It is also probable that these sublethal genetic factors can only break through the phenotype in conjunction with certain persistatic influences, including the mother's advanced age, which have an adverse effect on the formative power of the ovum.

Dystrophia Bullosa Hereditaria, Typus Maculatus.—Description of a family suffering from a disease characterized by formation of bullae without trauma, atrichia, hyperpigmentation, depigmentation, acrocyanosis, and dystrophic stigmata such as dwarfism, microcephaly, and short tapering fingers. The condition occurs exclusively in the males of the family, with recessive sex-linked inheritance. The genetic and cytoplasmatic factors regarded to have etiologic significance for Mongolism are discussed. Probably it is an irregularly dominant hereditary disease, with slight familial expression.

Developmental Dyslexia (Reading Disorders).—Fifteen types of children with reading disorders are described, and some of the pertinent problems are discussed. There is an original discussion especially of the didactic-therapeutic methods to correct the reading disorders.

Chronic Myocarditis.—Late sequelae of myocarditis are described in three patients who died of interstitial myocarditis with extensive fibrosis of the heart muscle. The possibility of a viral etiology is stressed. Such a virus myocarditis could therefore have a rapid fulminant course but could also take a protected course and finally lead to enlargement of the heart with decompensation.

Hyaline Membranes in the Lungs of Newborn Infants.—Material from 45 cases of hyaline membranes in premature infants was studied. It was concluded that factors conducive to the development of hyaline membranes in full-term babies will also have a certain effect in combination with prematurity. The development of transudation and hyaline membranes in fully developed children, according to the author, might be explained by the hypothesis that the physiological compression of the cranium is absent. This physiological compression commonly occurs in twins and in many children born by cesarean section or breech presentation and should result in insufficient stimulation of the cerebral center of the parasympathic vasomotor nerves.

Generalized Arteriosclerosis in Infants.—The authors could observe two cases of generalized arteriosclerosis in young infants. As always in such patients, the cardiac symptoms predominated. The localization of the pathologic changes even in the heart may be different.

Cardiovascular Deviations in Arachnodactyly.—A number of patients with arachnodactyly in whom a cardiovascular malformation existed at the same time are described.

Syndrome of Albright.—Following the description of a case of polyostotic fibrous dysplasia with abnormal pigmentation in a 6-year-old boy from British Guiana, a discussion of Albright's syndrome is given.

New England Journal of Medicine, Boston

Abstracted by Demetrius G. Traggis, M.D.

258, No. 9 (Feb. 27) 1958

* Infectious Hepatitis: Studies of Its Natural History and Prevention. R. Ward, S. Krugman, J. P. Giles, A. M. Jacobs, and O. Bodansky.—p. 407.

Vaccinia of the Lip: A Report of Two Cases, Including One with Superinfection of a Labial Herpetic Lesion. S. Kibrick and L. J. Kunz.—p. 421.

Air Embolism: A Hazard During Phlebotomy. P. J. Schmidt and S. V. Kevy.—p. 424.

Common Patterns of Water and Electrolyte Change in Injury, Surgery and Disease. F. D. Moore.—p. 427.

258, No. 13 (March 27) 1958

Porphyria: Report of Nine Cases Diagnosed in the Greater Hartford Area, Including a Family with Three Affected Members. M. J. Seide.—p. 630.

The Clinical Implications of Spinal-Fluid Lactic Dehydrogenase Activity. F. Wroblewski, B. Decker, and R. Wroblewski.—p. 635.

* Meningococcal Infections in Children. R. Koch and M. J. Carson.—p. 639.
Functional Disorders of the Urinary Bladder. H. Talbot.—p. 643.
Focal Central-Nervous-System Involvement Associated with Trichinosis: Report of a Case. H. Mavor.—p. 648.
Adrenocortical Hormones in Infections.—p. 662.

Infectious Hepatitis: Studies of Its Natural History and Prevention.—The authors report on infectious hepatitis in a mental institution. During a 5-year period, 1953-1957, there were 350 cases in the patients (106 cases in 1955) and 76 cases in personnel. The disease was mild, and there were no deaths. The patient census was between 3272 and 4478, and personnel averaged 964. There was no seasonal incidence. Highest rates were in the 15- to 20-year-old group and in the group over 50. Only five patients developed the disease within 45 days of admission (said to be upper limit of incubation period).

Two controlled studies on the use of γ-globulin were done. In the first, 0.01 ml. per pound was given intramuscularly to 1224 patients and there were 2988 controls. In the next 31 weeks 9 cases, or 7.4/1000, occurred in the γ-globulin group and 59, or 19.7/1000, in the control group. The experiment was repeated with use of 0.06 ml. per pound in 1182 patients with a control group of 1771 patients. During the next 39 weeks 2 cases, or 1.7/1000, occurred in the γ-globulin group, whereas 41 cases, or 22.5/1000, occurred in the controls.

An attempt was made to produce passive-active immunity. Eleven children were given γ-globulin, 0.06 ml. per pound intramuscularly and 30 minutes later were fed approximately twice their estimated 50% infectivity dose. Five others were given virus only. One of the eleven had mild hepatitis 54 days later. Four of the five controls developed jaundice. Of this total group of 16, there were 6 who were discharged, leaving 10. These 10 were challenged with virus five months later. The seven previously given both γ-globulin and virus did not develop hepatitis. One of three previously given virus only and who developed hepatitis the first time came down with hepatitis 44 days after challenge. Of four others acting as controls only one came down with hepatitis after being fed with the challenge virus, and that was 74 days later, which suggested secondary infection.

To try and determine incubation period, 16 patients were used. Ten were fed virus, and six, who were in intimate contact with these, were not. Hepatitis developed in 5 of the 10 (at 39, 41, 46, 60, and 71 days). Four of six not fed virus came down with hepatitis 60, 63, 57, and 71 days after the 10 were fed virus. Virus was found in the feces of patients 25 days after the feeding of virus and 2 or 3 weeks before onset of jaundice. There was no evidence of infection at this time by clinical or other laboratory studies.

Meningococcal Infections in Children.—The authors reviewed their cases of meningococcal infections from 1935 to 1956, particularly in the light of newer forms of treatment, especially the Waterhouse-Friderichsen syndrome. A total of 128 cases were admitted to the Los Angeles Children's Hospital, and 22 others were referred to a contagious disease hospital. Ninety-one of the one hundred twenty-eight had meningitis on admission. The remaining 37 had meningococcemia without cells in the CSF, and 16 of these were considered to show the Waterhouse-Friderichsen syndrome (fever, cyanosis, purpura, and shock).

Six died untreated (before days of specific therapy); eight treated with sulfonamide alone survived; of 39 treated with both sulfonamides and penicillin, 5 died; of 75 treated with multiple drugs (sulfonamides, penicillin, oxytetracycline, and streptomycin), 9 died. As far as age is concerned, 18.1% (of 66) of infants under 1 year died, 17.1% (of 35 cases) of children from 1 to 2 years old died, and 7.4% of those over 2 years of age died. Twelve of fifteen patients whose initial blood pressures were below 60 mm. Hg systolic died; 3 of 16 whose initial pressure was 60-50 mm. Hg systolic died, and 5 of 71 whose initial pressure was 78 mm. Hg systolic died. A total of 16 patients were seen with clinical diagnosis of Waterhouse-Friderichsen syndrome. Of seven treated before adrenal steroids were used (1953), one survived. Of nine treated after this period, only two survived, in spite of adequate steroids, vasopressors, whole blood, etc. Among 91 patients with meningitis there were only 5 deaths.

Subdural effusions developed in eight cases, prolonged fever being the principal signs of complication. Five patients had residual neurologic abnormality (all before introduction of subdural investigation in meningitis). Arthritis occurred in four children; iritis, in three, and pericarditis in two. Complications due to sulfonamide were few and not serious (fever in 1, skin rash in 1, leukopenia in 1, gross hematuria which rapidly cleared in 13).

In discussing their series the authors say that the sulfonamides are still the drugs of choice and that the mortality rate has not changed with the introduction of new antibiotics.

In spite of the development of the steroids, the mortality rate from Waterhouse-Friderichsen syndrome has not changed. Although, because of the relatively small number of patients developing subdural effusions, the authors do not recommend routine subdural taps, they point out that they have had no neurologic complications since they have performed them when indicated. They also state that, unlike the findings in other types of meningitis, familial infection occurs in 2% of cases, and, therefore, they recommend that all family contacts receive sulfonamides prophylactically.

Pediatriya, Moscow

Abstracted by Moses Grossman, M.D.

36, No. 2 (Feb.) 1958

Antibiotics in the Treatment of Toxic Diphtheria. K. V. Blumental.—p. 9.

Complex Treatment of Toxic Diphtheria. S. Y. Flexer.—p. 13.

The Course of Polyradiculoneuritis. E. I. Yampolskaya.—19.

Clinicobacteriological Parallels in Diphtheria. G. A. Khachiyan.—p. 25.

* Antitoxin Content in the Blood of Inoculated and Noninoculated Patients with Diphtheria. N. P. Kudryavtseva.—p. 30.

The Course of Diphtheria in Patients with an Incompleted Course of Antidiphtheric Vaccination. V. G. Grende.—p. 33.

Some Remarks on the Classification (Recommended by A. I. Titova) of Diphtheria Carriers and to Registration of the Efficacy of Measures in the Combat Against Them. G. A. Sudzhaev.—p. 39.

Antibiotic Sensitivity of Bacterial Flora in Children with Measles. N. M. Chireshkina and A. P. Kronrod.—p. 51.

Treatment of Bronchial Asthma in Children. N. A. Tyurin.—p. 65.

Age Correlations of Arterial and Venous Networks in the Pia Mater of the Big Hemispheres of the Brain in Postnatal Life. E. V. Kapustina.—p. 71.

* The Dynamics of Serum Proteins of the Blood in Scarlet Fever. T. S. Dadasheva.—p. 42.

Antitoxin Content in the Blood of Inoculated and Noninoculated Patients with Diphtheria.—The antitoxin content in the blood of 68 patients with diphtheria was determined at the Clinic of Children's Infections of the Kazan Medical Institute. Forty patients were inoculated, and twenty-eight were not inoculated. The antitoxin content in the blood of patients inoculated prior to introduction of the antidiphtheric serum was determined in concentrations from 0.03 to 0.3 A. U. (in 20 of 22 patients). In the noninoculated group the antitoxin titer was low—0.0005-0.005 A. U. (in 15 of 21 patients) and from 0.005 to 0.03 A. U. (in 6 out of 21). During the course of the disease the antitoxin titer in the blood of inoculated patients was considerably higher (6-11 A. U.) as compared with the noninoculated ones (5-8 A. U.).

After the introduction of the serum, the antitoxin titer increased in the blood till the fourth or fifth day and then decreased until the seventh or eighth day (the period of development of the serum disease). From the 9th to the 10th day the antitoxin titer increases again, reaching its maximum (8-11 A. U.) on the 10th-14th day. From the 15th-16th day gradual decrease of the antitoxin titer ensues.

The Dynamics of Serum Proteins of the Blood in Scarlet Fever.—Studies were performed on 56 patients (aged from 1 to 12 years) affected with scarlet fever. Protein fractions were studied in the dynamics of the disease by electrophoresis on paper. It was revealed that the regularity of fluctuations of general protein content and its fractions depended upon the phase, the severity of the disease, the presence of and the character of complications, the age of patients, and the treatment.

The acute stage of the disease was characterized by slight diminution of general protein and albumin content and by a pronounced increase of α_1- and α_2-globulins. Complications or concomitatnt diseases provoke shifts characteristic for the initial stage of the disease. These shifts are more pronounced if the complications are graver.

The severity of the course of scarlet fever is reflected in the increase of α_1- and α_2-globulins, and a more stable increase of γ-globulin. Fluctuations of the protein content in relation to the age of the patients is characterized by: (*a*) languid dynamics of protein shifts in children up to 3 years old, (*b*) more pronounced shifts in the α_2-globulin content in pre-school-age children as compared with juveniles, (*c*) a more regular increase of γ-globulin in juveniles. Administration of antibiotics in the early stages of scarlet fever noticably suppresses the increase of γ-globulins.

News and Comment

ANNOUNCEMENTS

Kenny Foundation Scholarship Program.—The Sister Elizabeth Kenny Foundation announces continuation of its program of postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of the neuromuscular diseases.

The Kenny Foundation Scholars will be appointed annually. Each grant will provide a stipend for a five-year period at the rate of $5,000 to $7,000 a year, depending upon the scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries regarding details of the program should be addressed to Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, Inc., 2400 Foshay Tower, Minneapolis 2.

Home for Asthmatic Children.—The Betty Bacharach Home, in association with the pediatric, medical, and psychiatric departments of the Jefferson Medical Center, has organized a unit for the treatment of intractable asthma in children. Children with perennial asthma of more than one year's duration and who are refractory to hyposensitization and other forms of medical treatment are eligible for admission.

The Betty Bacharach Home is ideally suited for this project. The asthmatic unit is a separate entity. Environmental control is excellent, and all facilities, including schooling, are available within the institution. Absecon Island, on which the Home is located, is a relatively pollen-free area.

Children from 5 to 15 years will be considered for admission. The Betty Bacharach Home will underwrite the cost for all children admitted to the unit. For further information contact Mr. Simon Lippman, Executive Secretary of the Betty Bacharach Home, Atlantic City, N. J.

Third-Year Residency in Pediatric Specialties.—A special residency providing longitudinal experiences in several of the subspecialties of pediatrics throughout the year is available to candidates who are graduates of a medical school in the United States or Canada and who have had an internship and two years of pediatric residency.

The resident may participate in the planning of his program. One or more days of each week may be spent in such specialties as cardiology, neurology, hematology, endocrinology, allergy, and psychiatry.

This program has been devised for the training of pediatricians to fill the gap now existing between the general practitioner type of pediatrician and the one highly skilled in a given specialty. It is thought that pediatricians with such additional training should (1) improve materially the quality of general pediatric practice, (2) serve more adequately as a consultant with the general practitioner, and (3) work effectively with the larger pediatric centers in the care of children who for one reason or another must receive a part of their medical care in such centers.

Appointments will be made for residencies beginning on July 1, 1959, on about March 1, 1959.

Applications may be made to Waldo E. Nelson, M.D., St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33.

Mary Putnam Jacobi Fellowship.—The Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2000, $1000 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, after which the second $1000 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances.

Applications for this Fellowship may be obtained from the secretary of the committee after Aug. 1, 1958, and must be returned before Feb. 1, 1959, with the following information: (1) curriculum vitae, (2) a statement from a physician of a recent physical examination, (3) transcripts of college and medical school records, (4) personal letters of recommendation from two or more physicians under whom the applicant has studied, (5) a statement by the applicant of the problems she proposes to investigate or the study she plans to undertake, (6) a statement from the person under whom she proposes to study of his or her interest in the subject, and (7) a recent photograph. All the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959. The secretary of the committee is Ada Chree Reid, M.D., 118 Riverside Drive, New York 24.

Course in Pediatric Dermatology.—Between the dates of Feb. 16 and 21, 1959, a five-day intensive course in pediatric dermatology will be offered by the Department of Pediatrics and the Division of Dermatology of Tulane University School of Medicine, New Orleans. It will cover infections of the skin, superficial and deep mycoses, congenital and acquired tumors, systemic and metabolic disorders, and allergic problems. Guest speaker will be Dr. Arthur C. Curtis, Professor of Dermatology, University of Michigan Medical School, Ann Arbor, Mich. There will be didactic lectures and demonstration of clinical material. Students will have an opportunity to learn at firsthand techniques applicable to diagnosis of skin diseases in childhood.

Postgraduate Seminar for Pediatricians.—The Eighth Annual Post-Graduate Seminar for Pediatricians will be conducted at St. Christopher's Hospital for Children, of the Pediatric Department of Temple University School of Medicine, Philadelphia, May 20-23, 1959. Half-day sessions will be devoted to various phases of pediatric medicine.

For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 3.

Directory of Pediatric Societies *

INTERNATIONAL

American Academy of Pediatrics

President: Dr. James C. Overall, 1924 Church St., Nashville 3, Tenn.
Vice-President: Dr. W. W. Belford, 420 Walnut St., San Diego 3, Calif.
Executive Secretary: Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill.
Time: Spring Session, April 13-15, 1959. Annual Meeting, Oct. 5-8, 1959.
Place: Spring Session, San Francisco. Annual Meeting, Palmer House, Chicago.

Ninth International Congress of Pediatrics

President: Dr. Allan Ross, P. O. Box 215, Westmount, Montreal 6.
Vice-President: Dr. Albert Guilbeault, P. O. Box 215, Westmount, Montreal 6.
Secretary-General: Dr. R. L. Denton, P. O. Box 215, Westmount, Montreal 6.
Place: Queen Elizabeth Hotel, Montreal. Time: July 19-25, 1959.

International Union for Child Welfare

President: Mr. Leonard W. Mayo, 1, rue de Varembé, Geneva, Switzerland.
Deputy President: Judge M. C. de Jong, 1, rue de Varembé, Geneva, Switzerland.
Secretary-General: Mr. D. Q. R. Mulock Houwer, 1, rue de Varembé, Geneva, Switzerland.

FOREIGN

Academy of Medicine, Toronto, Section of Paediatrics

Chairman: Dr. J. D. Bailey, 140 Brown's Line.
Secretary: Dr. John A. MacLean, 51 Eglinton Ave. East.
Place: Academy of Medicine. Meetings: Once a month.

Asociacion de Pediatrías Españoles

President: Dr. Rafael Ramos Fernández.
Vice-Presidents: Dr. Juan Bosch Marín and Dr. Ciriaco Laguna.
Secretary-General: Dr. Luis Navas Migueloa.
Treasurer: Dr. Angel Ballabriga.

Asociacion Pediatrica de Guatemala

President: Dr. María Isabel Escobar.
Vice-President: Dr. Victor A. Argueta von Kaenel.
Secretary: Dr. Antonio Berríos.
Treasurer: Dr. Carlos Monsón Malice.
Time: Second and fourth Thursdays of each month.

Australian Paediatric Association

President: Dr. M. T. Cockburn, 78 Brougham Pl., N. Adelaide.
Vice-President: Mr. K. B. Fraser, Ballow Chambers, Wickham Terrace, Brisbane.
Secretary: Dr. E. B. Sims, 80 Brougham Pl., Adelaide.
Place: Canberra. Time: Yearly in April.

British Paediatric Association

President: Dr. J. Forest Smith, 149 Harley St., London, W. 1.
Secretary: Dr. P. R. Evans, Institute of Child Health, Great Ormond St., London, W. C. 1.

Canadian Paediatric Society

President: Dr. J. Henri Charbonneau, 3095 Sherbrooke St. E., Montreal.
Secretary: Dr. J. A. P. Turner, 305 Bessborough Dr., Toronto 17.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Clinical Pediatric Society of Israel

Chairman: Dr. I. Heyman, Hadassah Municipal Hospital, Tel Aviv.
Committee: Dr. E. Schoenfeld, Tsahalon Government Hospital, Jaffa, Tel Aviv; Dr. Bernard E. Cohen, Tel Hashomer Government Hospital, Tel Litwinski.
Place: Hospital pediatric service throughout country. Time: Bimonthly.

Danish Pediatric Society

President: Dr. P. W. Braestrup, Amtssygehuset, Hellerup.
Vice-President: Dr. J. Vesterdal, Rigshospitalet, Copenhagen V.
Secretary: Dr. Folke Tudvad, Sundby Hospital, Copenhagen.
Place: Rigshospitalet, Children's Department, Copenhagen. Time: Monthly.

Deutsche Gesellschaft für Kinderheilkunde

President: Prof. E. Lorenz, Mozartgasse 14, Universitäts-Kinderklinik, Graz, Österreich.
Vice-President: Prof. K. Klinke, Moorenstr. 5, Kinderklinik d. med. Akademie.
Secretary: Prof. Dr. J. Jochims, Städt. Krankenhaus Süd, Kronsforder Allee 71/73, Lübeck.
President for 1959: Prof. A. Wiskott, München, Universitäts-Kinderklinik.
Place: München. Time: Aug. 31-Sept. 2, 1959.

Finnish Pediatric Association

President: Dr. Niilo Hallman, 11 Stenbäck St., Helsinki.
Vice-President: Dr. Bernhard Landtman, 45 Union St., Helsinki.
Secretary: Dr. Kalle Österlund, Hiihtäjäntie 6 B, Helsinki-Herttoniemi.
Place: Children's Hospital, Helsinki. Time: Every second month.

Greek Pediatric Society

President: Dr. Egle Inglessi, Marrommateon 29, Athens.
Secretary: Dr. Christos Kassimoe, Marni St. 4, Athens.
Place: Athens University. Time: Monthly.

Israel Pediatric Society

Chairman: Dr. B. Ostrowsky, Beth Harofe, 2 Wingate Ave., Haifa.
Secretary: Dr. F. Freundlich, Rambam Government Hospital, Haifa.

National Society of Child Health and Pediatrics of Turkey

President: Dr. Behçet Uz, Izmir.
Vice-President: Prof. S. S. Soysal, Istanbul.
Executive Secretary: Prof. I. Dogramaci, Research Institute of Child Health, Hacettepe Parki, Ankara.

Nederlandse Vereniging voor Kindergeneeskunde

President: Prof. Dr. W. K. Dicke, Wilhelmina Kinderziekenhuis, Nieuwe Gracht 137, Utrecht.
Honorary Secretary: Dr. H. Reerink, Sophia Kinderziekenhuis, Gordelweg 160, Rotterdam.
Place: Variable. Time: Three times a year.

Norsk Pediatrisk Selskap

President: Dr. E. Eyvind Ek, Oslo City Health Department, Oslo.
Vice-President: Dr. Martin Seip, Pediatric Department, Rikshospitalet, Oslo.
Secretary: Dr. K. Harnes, Pediatric Department, Rikshospitalet, Oslo.
Place: Pediatric Department, Rikshospitalet, Oslo. Time: Six or seven meetings a year.

Paediatric Society of New Zealand

President: Dr. S. L. Ludbrook, Lister Building, Victoria Street East, Auckland C. 1.
Vice-President: Dr. Murray McGeorge, Medical School, Dunedin.
Honorary Secretary: Dr. R. H. Caughey, 58 Symonds St., Auckland C. 1.
Honorary Treasurer: Dr. Alice M. Bush, 18 Symonds St., Auckland C. 1.
Place: Dunedin. Time: August.

PAEDIATRIC SOCIETY OF VICTORIA

President: Dr. J. H. Colebatch, 12 Collins St., Melbourne.
Honorary Secretary: Dr. H. N. B. Wettenhall, 41 Spring St., Melbourne.
Place: Lecture Theatre of the Royal Children's Hospital.
Time: Second Wednesday in each month at 8:00 p. m.

PHILIPPINE PEDIATRIC SOCIETY

President: Dr. Florencio N. Quintos, Philippine General Hospital, Manila.
Vice-President: Dr. Felix Estrada, St. Tomas University Hospital, Manila.
Secretary: Dr. Lino E. Lim, 235 Republic Supermarket, Rizal Ave., Manila.
Place: Physician's Club, Dewey Blvd., Manila. Time: Every two months; last Thursday of September, November, January, and March.

ROYAL SOCIETY OF MEDICINE, SECTION OF PAEDIATRICS

President: Dr. A. Doyne Bell.
Honorary Secretaries: Drs. Trevor P. Mann and H. H. Nixon, 1 Wimpole St., London, W. 1.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month from October to May.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. W. Tobler, Brunnadernrain 11, Bern.
Vice-President: Prof. M. Jaccottet, Av. de Rumine, Lausanne.
Secretary: Dr. J. Haas, Westl. Alpenstrasse 3, Burddorf.

SOCIEDAD ARGENTINA DE PEDIATRÍA

President: Dr. Rudolfo Kreutzer.
Secretary: Dr. Luis M. Cucullu.
Place: Sante Fè 1178, Buenos Aires.

SOCIEDAD BOLIVIANA DE PEDIATRÍA

President: Dr. Carlos Daza Meruvia.
Secretary: Dr. Cecilio Abela Deheza.
Place: S. C. I. S. P. Building. Time: Every Thursday.

SOCIEDAD CHIHUAHUENESE DE PEDIATRÍA

President: Dr. Alfonso Riuz Escalona.
Secretary: Dr. Armando G. Herrera.
Place: Hospital Infantil del Estado, Chihuahua, Chih., Mexico.

SOCIEDAD CHILENA DE PEDIATRÍA

President: Prof. Dr. Raúl Gantes A.
Secretary-General: Dr. Edmundo Cardemil.
Place: Medical Society, Merced 565, Santiago.

SOCIEDAD COLOMBIANA DE PEDIATRÍA

President: Dr. Alfonso Vargas Rubiano.
Vice-President: Dr. Darío Gutiérrez Laserna.
Secretary: Dr. Omar García Bustamante.
Treasurer: Dr. Alfonso Gutiérrez Reyes.

SOCIEDAD CUBANA DE PEDIATRÍA (FILIAL CIENFUEGOS)

President: Dr. Rafael Viego Delgado.
Secretary: Dr. Ramón Azaret Morón, Santa Cruz No. 167, Cienfuegos, Cuba.
Place: Colegio Médico. Time: 9:00 p. m., Wednesdays, six times a year.

SOCIEDAD ECUATORIANA DE PEDIATRÍA

President: Dr. Aldo Muggia.
Secretary: Dr. Nicolas Espinosa, Hospital Baca Ortiz, Quito, Ecuador, S. A.
Place: Hospital Baca Ortiz, Quito, Ecuador. Time: Monthly.

Sociedad de Pediatría de Concepción (Chile)

President: Dr. Daniel Campos, Hospital Clínico Regional, Concepción.
Secretary: Dr. Obdulia Jiménez, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month, April to December, inclusive.

Sociedad de Pediatría del Litoral

President: Dr. Raul Bruera.
Vice-President: Dr. Isidoro Slullitel.
Secretary-General: Dr. Elsa Galimany.

Sociedad de Pediatría y del Atlantico

President: Dr. Atilio Marino.
Vice-President: Dr. Helena Uribe de Jimenez.
Secretary-Treasurer: Dr. Herando Barrios-Angulo.

Sociedad Uruguaya de Pediatría

President: Dr. Julio R. Mareos, Av. 8 de Octubre 2710, Montevideo.
Secretary: Dr. Norma Curbelo Gamba, Enrique Muñoz 932, Montevideo.
Place: Av. Agraciada 1464, piso 13, Montevideo. Time: First and third Wednesdays of each month.

Sociedad Venezolana de Puericultura y Pediatría

President: Dr. Miguel Raga.
Vice-President: Dr. Jorge Lizarraga.
Secretary: Dr. Herman Mendez C.

Sociedad Yucateca de Pediatría

President: Dr. Humberto Perz Concha.
Secretary: Dr. Prudencio Ruiz Salazar.
Treasurer: Dr. Jorge Antiveros Andrade.

Sociedade Meneira de Pediatría

President: Dr. Agostinho Fernandes.
Secretary: Dr. Celio Marques Scotti.

Sociedade de Pediatria da Bahia

President: Dr. Elysio Pereira de Atbayde.
Secretary: Dr. Eliezer Audiface.

Sociedade de Pediatria de Pernambuco

President: Dr. Antonio Aureliano.
Secretary: Dr. Claudia Figueiredo.

Sociedade de Pediatria do Rio Grande do Sul

President: Dr. Francisco Talaia de Moura.
Secretary: Dr. Enio Pilla.

Sociedade Portuguesa de Pediatria

President: Prof. Fonseca e Castro, Praça do Liege 101, Porto.
Vice-President: Prof. Carlos Salazar de Sousa, Avenida da Republica 64, Lisbon.
Secretary: Dr. Mario Cordeiro, Avenida do Restelo 17, Lisbon.
Place: Lisbon. Time: Once a month.

Sociedade de Puericultura e Pediatria do Maranbao

President: Dr. Ordorico Amaral de Mattos.
Secretary: Dr. Joao Mohana.

Societa Italiana di Pediatria

President: Prof. Giuseppe Caronia.
Vice-Presidents: Prof. Mario Cotellessa and Prof. Gaetano Salvioli.
Secretary: Prof. Rolando Bulgarelli.

SOCIÉTÉ FRANCAISE DE PÉDIATRIE

President: Prof. Paul Rohmer, 6 Quai Foch, Strasbourg.
Vice-President: Prof. Raymond Turpin, 194 Avenue Victor Hugo, Paris (XVI).
Secretary: Prof. Maurice Lamy, 94 Rue de Varennes, Paris (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sèvres, Paris (XV). Time: Third Tuesday of every month.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Rémi Archambault.
Vice-President: Dr. Claude Leonard.
Secretary: Dr. Paul Dagenais-Perusse, La Société de Pédiatrie de Montréal, Inc.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Prof. Marcel Lelong, 197 Boulevard St-Germain (VII).
Secretary: Prof. Maurice Lamy, 94 Rue de Varenne (VII).
Place: Hôpital des enfants-malades, 149 Rue de Sevres (XV). Time: 4:00 p. m., third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUÉBEC

President: Dr. Antoine Larue, 1193 des Érables, Québec.
Vice-President: Dr. Antoine Bélanger, 31 Guénette, Lévis.
Secretary: Dr. Maurice Richard, 1215 des Pins, Sillery.
Place: Québec City. Time: First week of May and November.

SOCIÉTE SUISSE DE PÉDIATRIE

President: Prof. M. Jaccottet, Hôpital Cantonal, Lausanne.
Vice-President: Prof. Willys, Zurich.
Secretary: Dr. E. Juillard, Hôpital Cantonal, Lausanne.
Time: June.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

President: Dr. B. Epstein, 104 van Riebeeck Building, Pretoria.
Secretary: Dr. E. Fasser, 201 Medical Centre, Pretoria.

SWEDISH PEDIATRIC SOCIETY

President: Prof. Bo Vahlquist, Pediatriska Kliniken, Akademiska Sjukhuset, Uppsala.
Secretary: Dr. Marcel d'Avignon, Barnkliniken, Karolinska Sjukhuset, Stockholm.
Place: Svenska Läkaresällskapet, Stockholm. Time: Second Friday of October, December, February, and May.

UNITED STATES

National

AMERICAN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. Wyman C. Cole, 1063 Fisher Building, Detroit 2.
Vice-Chairman: Dr. E. Revere Cole, Sacramento, Calif.
Secretary: Dr. Arild Hansen, Galveston, Texas.
Place: Atlantic City, N. J. Time: June, 1959.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Joseph Stokes Jr., Children's Hospital of Philadelphia, Philadelphia 46.
Vice-President: Dr. W. L. Bradford, 260 Crittenden Blvd., Rochester 20, N. Y.
Secretary: Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washington 8, D. C.
Place: The Inn, Buck Hill Falls, Pa. Time: May 6-8, 1959.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Sydney S. Gellis, 818 Harrison Ave., Boston 18.
Vice-President: Dr. Margaret Smith, 550 1st Ave., New York 16.
Secretary: Dr. Clark West, Children's Hospital, Cincinnati 29.
Place: The Inn, Buck Hill Falls, Pa.

Sectional

Intermountain Pediatric Society

President: Dr. R. H. Wakefield, 410 N. University Ave., Provo, Utah.
Vice-President: Dr. Wesley H. Anderson, 39 Virginia Professional Building, Ogden, Utah.
Secretary: Dr. Thales H. Smith, 220 N. University Ave., Provo, Utah.

New England Pediatric Society

President: Dr. Alice Whittier, 143 Neal St., Portland 4, Maine.
Vice-President: Dr. Sidney Gellis, Boston City Hospital, Boston.
Secretary: Dr. Harry Shwachman, Children's Hospital, Boston.
Place: Three meetings in Boston; spring meeting, variable. Time: Four meetings per year.

North Pacific Pediatric Society

President: Dr. S. Gorham Babson, 1107 S. W. 13th, Portland 5, Ore.
President-Elect: Dr. Norman Murphy, Seattle
Secretary: Dr. Peter Sophn, 3195 Granville St., Vancouver, B. C.
Place: Seattle. Time: April.

Northwestern Pediatric Society

President: Dr. John D. Bailey, Box 849, Rapid City, S. D.
Vice-President: Dr. H. M. Medovy, University of Manitoba, Winnipeg, Canada.
Secretary-Treasurer: Dr. John C. O'Brien, 868 Lowry Medical Arts Building, St. Paul.

Rocky Mountain Pediatric Society

President: Dr. Alfred Hicks II, 1592 Madison St., Denver.
Vice-President: Dr. James Watson, Colorado Springs, Colo.
Secretary: Dr. Frank J. Cozzetto, 2401 E. 6th Ave., Denver 6.
Place: To be announced. Time: May, September, November, March.

Southwestern Pediatric Society

President: Dr. Wendell Redfern, 125 Glen Oaks, Glendale, Calif.
Vice-President: Dr. Chester Tancredi, 411 Thorn St., San Diego, Calif.
Secretary: Dr. Robert Shirley, 11633 San Vicente Blvd., Los Angeles 49.
Place: University Club of Los Angeles. Time: Bimonthly on third Wednesday of month.

Western Society for Pediatric Research

President: Dr. James F. Bosma, 1940 S. 2d East, Salt Lake City.
Vice-President: Dr. William Deamer, Dept. of Pediatrics, University of California, San Francisco.
Secretary: Dr. Robert H. Alway, Stanford School of Medicine, San Francisco.
Place: Salt Lake City.

State

Academy of Pediatrics, Indiana Chapter

President: Dr. William M. Browning, 3740 Central Ave., Indianapolis 5.

Alabama State Pediatric Society

President: Dr. Jerome A. Weaver, 715 1st Ave. S., Birmingham.
Vice-President: Dr. Robert O. Harris III, 2151 Grant St., Mobile.
Secretary-Treasurer: Dr. J. M. Humphries, 2115 Warrior Rd., Birmingham.

Arizona State Pediatric Society

President: Dr. B. P. Starts, 1018 N. Country Club Rd., Tucson.
Secretary: Dr. Jack H. Demlow, 130 S. Scott, Tucson.
Time: Spring and fall.

California Medical Association, Section on Pediatrics

President: Dr. Sidney Rosin, 6230 Wilshire Blvd., Los Angeles.
Secretary: Dr. Percy H. Jennings Jr., 1650 Walnut St., Berkeley 9.

Florida State Pediatric Society

President: Dr. Henry Morton, 1950 Arlington St., Sarasota.
Vice-President: Dr. Burns A. Dobbins, 120 E. Broward Blvd., Fort Lauderdale.
Secretary: Dr. Harry M. Edwards, 113 E. Broadway, Ocala.
Time: Spring and fall.

Georgia Pediatric Society

President: Dr. Edwin R. Watson, 745 Pine St., Macon.
Vice-President: Dr. Richard L. Sehley Jr., 114 W. Gaston St., Savannah.
Secretary-Treasurer: Dr. LeRoy Antrobus, 3130 Maple Dr., N. E., Atlanta.
Place: Atlanta (October meeting). Time: October and April.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Abe S. Brown, 58 Central Ave., Waterbury.
Secretary: Dr. Thomas Monagan, 195 Grove St., Waterbury.
Place: Variable. Time: Two or three meetings a year.

Illinois State Medical Society, Section on Pediatrics

President: Dr. Lawrence Breslow, 2424 W. Peterson, Chicago 45.
Secretary: Dr. Homer Weir, Rockford.
Place: Chicago. Time: May, at time of state meeting.

Iowa Pediatric Society

President: Dr. Guido J. Sartor, Mason City.
Vice-President: Dr. John C. McQueen, Pediatric Department, State University of Iowa, Iowa City.
Secretary: Dr. Ralph E. Dyson, 3200 University Ave., Des Moines 11.
Place: Spring meeting in conjunction with the Iowa State Medical Society meeting; fall meeting in September at University Hospital, Iowa City.

Kansas State Pediatric Society

President: Dr. Hilbert P. Jubelt, 1200 Fremont St., Manhattan.
Vice-President: Dr. Thomas C. Hurst, 405 K. F. H. Building, Wichita.
Secretary: Dr. William H. Crouch, 306 Medical Arts Building, Topeka.
Place: Emporia. Time: 9:30 a. m., first Saturday after Labor Day.

Kentucky Pediatric Society

President: Dr. Caroline Scott, 200 W. 2d. St., Lexington.
Vice-President: Dr. Carolyn McKinlay, Glasgow.
Secretary: Dr. Howard Rippy, 310 W. 2d. St., Lexington.
Place: Lexington. Time: April.

Louisiana State Pediatric Society

President: Dr. Bertha Wexler, New Orleans.
President-Elect: Dr. Thomas E. Strain Sr., Shreveport.
Secretary: Dr. Dorothy J. York, 2902 Napoleon Ave., New Orleans.
Place: New Orleans. Time: May 3, 1959.

Michigan State Medical Society, Pediatric Section

President: Dr. Harry A. Towsley, University Hospital, 1313 Ann St., Ann Arbor.
Secretary: Dr. Charles Frank Payton, 611 S. Washington, Royal Oak.

Montana Pediatric Society

President: Dr. John Halseth, Great Falls.
Secretary: Dr. George Barmeyer, Missoula.
Place: Helena. Time: March, 1959.

Nebraska Pediatric Society

President: Dr. E. S. Wegner, 724 Sharp Building, Lincoln.
Vice-President: Dr. Robert Grant, 909 Sharp Building, Lincoln.
Secretary: Dr. Gilbert Schreiner, 125 N. 38th St., Omaha.
Place: Omaha. Time: Third Thursday of each month at the Children's Memorial Hospital.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Robert F. Wilson, 113 Locust St., Dover.
Secretary: Dr. Arthur E. Laidlaw, Keene Clinic, Keene.
Place: Variable. Time: Variable.

NEW MEXICO PEDIATRIC SOCIETY

President: Dr. Albert S. Lathrop, P. O. Box 912, Coronado Building, Santa Fe.
Vice-President: Dr. Guy E. Radar, 4120 Silver S. E., Albuquerque.
Secretary: Dr. Carol K. Smith, P. O. Box 2056, Coronado Building, Santa Fe.
Place: Variable. Time: Four times a year.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Leroy J. Butler, Winston-Salem.
President-Elect: Dr. Thomas A. Hensen, Greensboro.
Secretary-Treasurer: Dr. John F. Lynch Jr., Greensboro.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Fred Adams, 157 Pine St., Spartanburg.
Vice-President: Dr. C. Guy Castle Jr., 1417 Gregg St., Columbia.
Secretary: Dr. Charles Zemp, 1105 Lyttleton St., Camden.
Place: Columbia and Myrtle Beach. Time: September and May of each year.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Gilbert Levy, Memphis.
Vice-President: Dr. Jack Chesney, Knoxville.
Secretary: Dr. Robert G. Jordan Jr., Le Bonheur Children's Hospital, Memphis.
Place: Memphis. Time: May 18, 1959.

TEXAS PEDIATRIC SOCIETY

President: Dr. Bruce A. Knickerbocker, 3403 Hall St., Dallas 4.
Secretary: Dr. James N. Walker, 5216 W. Freeway, Fort Worth 7.
Place: Houston. Time: October, 1959.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Harry Cox, 113 Fauquier St., Portsmouth.
Vice-President: Dr. Robert H. Cox jr., Allied Arts Building, Lynchburg.
Secretary: Dr. O. Watts Booth, 87 29th St., Newport News.

WISCONSIN STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

Chairman: Dr. E. H. Pawsat, Fond du Lac.
Vice-Chairman: Dr. Samuel E. Kohn, Milwaukee.
Secretary: Dr. J. R. Schroder, Janesville.
Delegate: Dr. K. J. Winters, Wauwatosa.
Alternate Delegate: Dr. F. Mellencamp, Milwaukee.

Local

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. C. T. J. Dodge, 15457 Euclid Ave. (12).
Secretary: Dr. Beulah Wells, 10515 Carnegie Ave. (6).
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February, and March.

AKRON PEDIATRIC SOCIETY

President: Dr. Edward A. Sawan, 111 W. State St.
Vice-President: Dr. John Norman, 513 W. Market St.
Secretary: Dr. Frederick Fiedorek, 2695 N. Haven Blvd., Cuyahoga Falls, Ohio.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

President: Dr. Melchijah Spragins, 102 Alleghany Ave., Towson 4, Md.
Vice-President: Dr. Harry H. Gordon, Sinai Hospital of Baltimore, Inc., Monument St. and Rutland Ave. (5).

Secretary: Dr. B. M. Debuskey, 2501 W. Belvedere Ave.
Place: 1211 Cathedral St. Time: Second Tuesday in November, January, and March at 8:30 p. m.

Baton Rouge Pediatric Society

President: Dr. Clifton Morris, Roumain Building.
Vice-President: Dr. John Ray Powers, 3347 Government St.
Secretary: Dr. Stephen Madey, 1401 N. Foster Dr.
Time: Quarterly as called.

Bronx Pediatric Society

President: Dr. Jess Diamond, 1900 Grand Concourse (57).
Vice-President: Dr. Archie Cohen, 2280 Grand Ave.
Secretary: Dr. Arthur A. Goldfarb, 1150 Grand Concourse.
Place: Morrisania Hospital. Time: Second Wednesday of each month, 8:30 p. m.

Brooklyn Academy of Pediatrics

President: Dr. Adolph Emerson, 7721 Ridge Blvd. (9).
Vice-President: Dr. Joseph Pincus, 881 Washington Ave. (25).
Secretary: Dr. Morris Steiner, 456 E. 19th St. (26).
Place: Hotel Granada. Time: Fourth Wednesday of each month, 8:45 p. m.

Buffalo Pediatric Society

President: Dr. Norman C. Bender, 227 Colvin Ave.
Vice-President: Dr. Thomas S. Bumbalo, 354 Lincoln Parkway.
Secretary: Dr. Lois J. Plummer, 131 Linwood Ave.
Place: Alternating Buffalo Children's Hospital and Edward J. Meyer Memorial Hospital.
Time: Fall, winter, and spring and on call.

Central Illinois Pediatric Society

President: Dr. Howard R. Miller, 114 Stratford, Peoria.
Vice-President: Dr. Paul P. Pierce, 1900 Brown St., Alton.
Secretary-Treasurer: Dr. Richard E. Dukes, Carle Hospital Clinic, Urbana.
Place: Variable. Time: Fall and spring.

Central New York Pediatric Club

President: Dr. George R. Murphy, Elmira.
Vice-President: Dr. Herbert Soule Jr., Rochester.
Secretary: Dr. Fred W. Bush, 325 Park Ave., Rochester 7.
Place: Variable. Time: Spring and fall.

Central Ohio Pediatric Society

President: Dr. William Newton, Children's Hospital, Columbus.
Secretary: Dr. Robert Batterson, 350 E. Broad St., Columbus.
Place: Maramour Restaurant. Time: Fourth Wednesday of each month.

Chicago Pediatric Society

President: Dr. Noel G. Shaw, 2901 W. Central St., Evanston, Ill.
Vice-President: Dr. Raymond R. Grissom, 715 Lake St., Oak Park, Ill.
Secretary: Dr. James A. Conner, 101 S. Garfield, Hinsdale, Ill.
Place: Children's Memorial Hospital. Time: 8:30 p. m., third Tuesday in each month, October to May.

Cincinnati Pediatric Society

President: Dr. Harold A. Cassady, 2728 Erie Ave.
Vice-President: Dr. Carl V. Ochs, 2727 Madison Rd.
Secretary: Dr. Carl A. Koch, 3511 Glenmore Ave.
Place: Children's Hospital. Time: Quarterly.

Cleveland Academy of Medicine, Pediatric Section

Chairman: Dr. Robert Hauver, 10515 Carnegie Ave.
Secretary: Dr. William Herman, 10300 Carnegie Ave.

Corpus Christi Pediatric Society

President: Dr. Norman C. Woody, 515 Elizabeth St.
Vice-President: Dr. Joseph Oshman, 1010 Ohio.
Secretary: Dr. Mary McCaskey, 1001 Louisiana.
Time: Fourth Wednesday, every two months.

Dallas Pediatric Society

President: Dr. Logan W. McWhinney, 6115 LaVista.
Secretary-Treasurer: Dr. Ben W. Denny, 1511 N. Beckley.
Place: Children's Medical Center. Time: 6:30 p. m., first Thursday in each month.

Des Moines Pediatric Society

President: Dr. Charles L. Burr, 5701 Hickman Ave.
Vice-President: Dr. James E. Dyson, 3200 University Ave.
Secretary-Treasurer: Dr. Glen E. Nielsen, 3009 Ingersoll Ave.
Place: Des Moines Golf and Country Club. Time: Fourth Tuesday of each month, October to May.

Detroit Pediatric Society

President: Dr. Charles G. Jennings, 14827 E. Jefferson (15).
Vice-President: Dr. Douglas L. Wake, 1307 S. Washington, Royal Oak, Mich.
Secretary: Dr. Irving Burton, 14627 E. 7 Mile Rd.
Place: Variable. Time: Variable.

Fort Worth Pediatric Society

President: Dr. Harry Womack, 1424 W. Peter Smith.
Secretary: Dr. Blanche O. Terrell, 1425 Pennsylvania Ave.
Place: Variable. Time: Fourth Friday of each month.

Hinterland Pediatric Society

President: Dr. John Wilcox, 152 Nemaha St., Pomona, Calif.
Vice-President: Dr. Edward Zeman, 3616 Main St., Riverside, Calif.
Secretary: Dr. George A. Chalfant, 1086 San Bernardino Rd., Upland, Calif.
Place: Alternating San Bernardino, Riverside, and Pomona. Time: Fourth Tuesday of February, May, September, and November.

Honolulu Pediatric Society

President: Dr. Clifford K. Kobayashi, 1423 Kalakaua.
Secretary-Treasurer: Dr. Donald I. B. Char, Children's Hospital.
Recording Secretary: Dr. Robert G. Dimler, 539 Kailna Rd., Lanikai, Oahu.
Place: Members' homes. Time: 6:30 p. m., third Thursday of each month.

Houston Pediatric Society

President: Dr. Robert A. Gardner, 4006 Montrose.
Vice-President: Dr. Helen G. Schaffer, 2905 La Branch.
Secretary: Dr. Robert H. Hardie, 1701 S. Shepherd Dr.
Place: River Oaks Country Club. Time: Fourth Tuesday of each month.

Kansas City Southwest Pediatric Society

President: Dr. Bailey C. Andrees, 315 Nichols Rd., Kansas City, Mo.
Vice-President: Dr. H. P. Jubelt, 111 S. 4th St., Manhattan, Kans.
Secretary: Dr. G. W. Wise, Plaza Parkway Building, Kansas City, Mo.
Place: University Club, Kansas City, Mo. Time: Quarterly, on call.

Long Beach Pediatric Society

President: Dr. James Fowler, 2240 Pacific Ave.
Vice-President: Dr. Milton Katz, 1868 Pacific Ave.
Secretary: Dr. David M. Rozran, 911 E. San Antonio Dr.
Place: University Club, 1150 E. Ocean Blvd. Time: First Tuesday of each month.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Wendell M. Redfern, 720 N. Brand Blvd., Glendale (3).
Vice-President: Dr. Morris J. Naiditch, 239 S. La Cienega Blvd., Beverly Hills, Calif.
Secretary-Treasurer: Dr. Neil N. Litman, 5830 Overhill Dr. (43).
Place: Los Angeles County Medical Association Building. Time: Second Thursday in September, November, January, March, and May.

Louisville Pediatric Society

President: Dr. Edwin Paul Scott, 3610 Lexington Rd.
Vice-President: Dr. Martin J. Harris, Francis Building, 4th & Chestnut Sts.
Secretary: Dr. Paul Patrick Hess, Floyd County Bank Building, New Albany, Ind.
Place: Variable. Time: Four times a year.

Medical Society of the County of Kings, Brooklyn Pediatric Section

President: Dr. David Dragutsky, 1466 49th St.
Vice-President: Dr. Abraham Gilner, 303 Beverly Rd., Brooklyn 18.
Secretary: Dr. Saul Starr, 1822 Ave., H.
Place: King's County Medical Society Building. Time 9:00 p. m., fourth Monday of October, November, January, March, and April.

Medical Society of the District of Columbia, Section of Pediatrics

President: Dr. George Maksim 1418 Good Hope Rd. S. E., Washington, D. C.
Vice-President: Dr. W. A. Howard, 1517 30th St. N. W., Washington, D. C.
Secretary: Dr. John E. Cassidy, 9911 Old Georgetown Rd., Bethesda, Md.
Place: Medical Society Building. Time: On call.

Memphis Pediatric Society

President: Dr. M. Blake Arnoult, 4720 Poplar Ave.
Vice-President: Dr. Kinsey M. Buck, 1193 Madison Ave.
Secretary: Dr. William W. Mason, 3314 Poplar Ave.
Place: Memphis Country Club. Time: Second Tuesday of March, June, September, and December.

Miami Pediatric Society

President: Dr. Howard A. Engle, 975 Arthur Godfrey Rd.
Secretary-Treasurer: Dr. Charles Rosenfeld, 1500 S. W. 22nd St.

Milwaukee Pediatric Society

President: Dr. Helen Zillmer, 425 E. Wisconsin Ave.
Vice-President: Dr. Sam Rosenberg, 2303 N. 49th St.
Secretary: Dr. Ted Buszkiewicz, 3333 S. 27th St.
Place: University Club. Time: Second Wednesday of alternate months.

Mobile Pediatric Society

President: Dr. Robert O. Harris III, 2 N. Florida St.
Secretary: Dr. James W. Coker Jr., 1367 Government St.
Place: Variable. Time: Quarterly.

Montgomery County Pediatric Society

President: Dr. C. E. Robert Parker, 335 S. Ripley St., Montgomery, Ala.
Vice-President: Dr. William R. Britton, 133 S. Union, Montgomery.
Secretary: Dr. William B. Brock, 1709 Pipe St., Montgomery.
Place: Montgomery. Time: Quarterly.

Nashville Pediatric Society

President: Dr. Harry M. Estes, 1924 Hayes St.
Secretary: Dr. Ray L. Dubuisson, Formosa Building, Hillsboro Dr.
Place: Members' homes. Time: Third Thursday of each month.

NASSAU PEDIATRIC SOCIETY

President: Dr. Selma Buchbinder, 295 Harvard Ave., Rockville Centre, N. Y.
Vice-President: Dr. James Dick, 87 Meridian Rd., Levittown, N. Y.
Treasurer: Dr. David Posner, 98 Wolcott Rd., Levittown, N. Y.
Place: Felice's Restaurant, Westbury, Long Island. Time: Second Monday in February, April, June, October, and December.

NEW ORLEANS PEDIATRIC SOCIETY

President: Dr. Norman Robinson, 1520 Louisiana Ave.
Vice-President: Dr. Richard P. Vieth, 3411 Coliseum St.
Secretary: Dr. Gene C. Hassinger, 1448 Louisiana Ave.
Treasurer: Dr. Thomas Furlowe, 2110 Foy St.
Place: Variable. Time: Six times a year.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. Benjamin Kramer, 60 Plaza St., Brooklyn.
Secretary: Dr. Henry L. Barnett, 535 East 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St., New York.
Time: 8:30 p. m., every second Thursday of October through May.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. Samuel Hurwitz, 6200 Geary Blvd., San Francisco 21.
Vice-President: Dr. Percy Jennings Jr., 1650 Walnut St., Berkeley 9.
Secretary: Dr. Agnes G. Plate, 2445 Ocean Ave., San Francisco 27.
Place: Variable. Time: Every three months.

NORTHERN OHIO PEDIATRIC SOCIETY

President: Dr. Leon H. Dembo, 10515 Carnegie Ave., Cleveland 6.
Secretary: Dr. Hugh Leslie Jr., 5867 Mayfield Rd., Cleveland 24.
Place: Babies and Childrens Hospital, Cleveland. Time: March, May, October, and December.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Jerome D. Shaffer, 1200 North Walker.
Secretary: Dr. Eric B. Meador, 2548 N. W. 23d.
Place: Variable. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Hubert A. Royster Jr., 748 S. Latch's Lane, Merion, Pa.
Vice-President: Dr. Rachel Ash, 5636 Pine St. (43).
Secretary: Dr. Robert H. High, 400 Kent Rd., Cynwyd, Pa.
Place: College of Physicians. Time: Second Tuesday of each month, October to May.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Robert Macdonald, 448 Brownsville Rd. (10).
Vice-President: Dr. Bernard I. Michaels, 3500 5th Ave. (13).
Secretary: Dr. James Reilly, 2331 Laketon Rd. (21).
Place: Variable. Time: January, March, May, September, November.

QUEENS PEDIATRIC SOCIETY

President: Dr. Ben Goldsmith, 4027 Murray St., Flushing 54, N. Y.
Vice-President: Dr. Fred Castrovinci, 3357 75th St., Jackson Heights 72, N. Y.
Secretary: Dr. Emanuel Fletcher, 14010 Franklin Ave., Flushing 55, N. Y.
Place: Seminole Club. Time: Second Tuesday of February, April, October, and December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Helen L. Morton, 5011 Forest Hill Ave.
Vice-President: Dr. Thomas S. Chalkley, 3011 Monument Ave.
Secretary: Dr. Lillian C. Lindemann, 4708 Cary St. Rd.
Place: Richmond Memorial Hospital. Time: Third Thursday of the month, September through May.

St. Louis Pediatric Society

President: Dr. Alfred S. Schwartz.
Vice-President: Dr. James P. King.
Secretary: Dr. Mirriam H. M. Pennoyer, 500 Kingshighway Blvd.
Place: Medart's Restaurant. Time: 7:00 p. m., second Thursday of each month from September to May, inclusive.

San Antonio Pediatric Society

President: Dr. B. B. Shaver, Medical Professional Building.
Vice-President: Dr. J. Newton, 302 Craydon.
Secretary: Dr. Scott Stewart, 123 Ogden Lane.
Place: Variable. Time: Second Wednesday of each month.

Santa Barbara Pediatric Society

President: Dr. Louis Needles, County Health Department.
Secretary: Dr. Newton Wayland, 1515 State St.
Place: Variable. Time: On call.

Seattle Pediatric Society

President: Dr. Ward Chesley, 900 Boylston.
Secretary-Treasurer: Dr. Stanley V. Stamm, 8016 35th, N. E.
Place: College Club. Time: 7:30 p. m., third Friday of each month from September to June.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. James W. Skinner, 612 Elm St., St. Joseph, Mich.
Secretary-Treasurer: Dr. George H. Lowrey, University Hospital, Department of Pediatrics, Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Spring.

Waco Pediatric Society

President: Dr. J. M. Garrett, 1408 Austin Ave.
Secretary: Dr. Charles Shellenberger, 2425 Washington Ave.
Place: Hillcrest Hospital. Time: Last Tuesday of each month.

Westchester County Academy of Medicine, Pediatric Section

President: Dr. A. H. Hardy, 146 Prospect Ave., Mt. Vernon.
Secretary: Dr. Irving Nelson, 150 E. Hartsdale Ave., Hartsdale, N. Y.
Place: Pforscheimer Memorial Building, Harrison, N. Y.
Time: Quarterly.

Western Michigan Pediatrics Society

President: Dr. John W. Thompson, 833 Lake Drive, S. E., Grand Rapids.
Vice-President: Dr. Ethon L. Stone, 721 17th St., Jackson.
Secretary: Dr. Donald C. Johns, 655 Broadview S. E., Grand Rapids.
Place: Grand Rapids in November and March. Other west Michigan cities in September and June.

Wichita Pediatric Society

President: Dr. William F. McGuire.
Secretary: Dr. Katherine Pennington, Sedgwick County Medical Society, Schwiter Building, Wichita, Kan.
Place: Homes of members. Time: 8:30 p. m., first Thursday, October through May.

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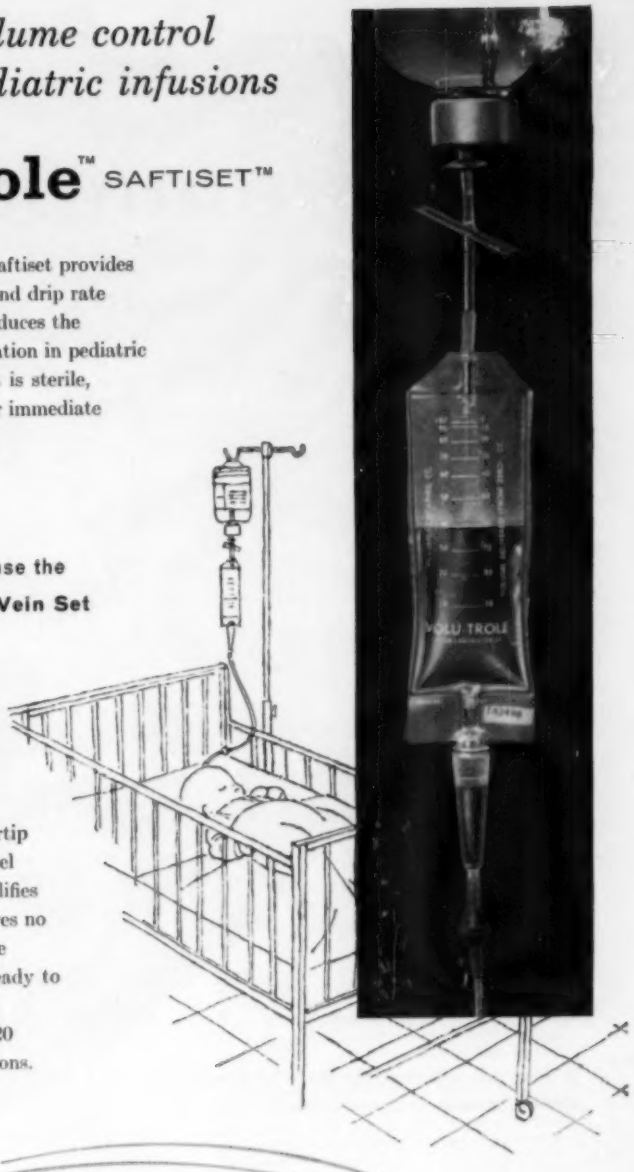

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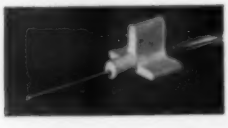

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REFERENCES: 1. Miller, J. H., et al.: Am. J. Dig. Dis. 3:229-231, 1958.
2. Swartzwelder, J. C., et al.: A.M.A. Arch. Int. Med. 101:658-61, 1958.
3. Frye, W. W., et al.: Am. J. Trop. Med. Hyg. 6:890-93, 1957.
4. Swartzwelder, J. C., et al.: J.A.M.A. 165:2063-67, 1957.

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For these reasons—as well as because aspirin is the most widely used drug in the world, and one of the safest and most effective drugs in the entire range of medicine—St. Joseph Aspirin For Children has long been an aspirin of choice whenever salicylate therapy is indicated in infancy and childhood.

A palatable aspirin tablet of unique excellence

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How to win friends ...

The Aspirin that
Tastes So Good.

The Flavor Remains Stable
down to the last tablet.

25¢ Bottle of 48 tablets.

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KIDS LOVE 'EM*

*WORMS HATE 'EM

No fasting • No special diets • No purging

The new Piperazate Wafers, utilizing insoluble piperazine *phosphate*, provide short, pleasant piperazine treatment for intestinal helminths. For pinworm, *only one dose a day* for just *one week* is required; for roundworm, *a single dose*.

Kids love the cool, tasty mint flavor of Piperazate Wafers. There is no possibility of spillage or variation in the size of the dose. And the use of Piperazate avoids the high incidence – 35-50% – of nausea, vomiting and diarrhea which may be associated with gentian violet therapy.[1]

Piperazate assures a 90% cure rate in one week's treatment of pinworm[2] and an 85% cure rate in one day's treatment of roundworm.[3]

One Week Dosage for Pinworm

Children 15-30 lbs. . . . 1 Wafer
Children 31-60 lbs. . . . 2 Wafers
Children 61 lbs. and over . . . . . 4 Wafers

To be sucked or chewed before breakfast for 7 consecutive days.

One Day Dosage for Roundworm

Children 20-30 lbs. . . . 3 Wafers
Children 31-40 lbs. . . . 4 Wafers
Children over 40 lbs. and adults . . . . . 7 Wafers

To be taken at one time on one day only.

Piperazate* Wafers

piperazine phosphate, Leeming, 500 mg.

Supplied: In packages of 28 Wafers

1. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, Macmillan, 1955, p. 1153. 2. Brown, H. W., *et al.*: J.A.M.A. *161*:515 (June) 1956. 3. Hoekenga, M. T.: World M. J. *3*:299 (Sept.) 1956.

*TRADEMARK

Thos. Leeming & Co. Inc. 155 East 44th Street, New York 17, N. Y.

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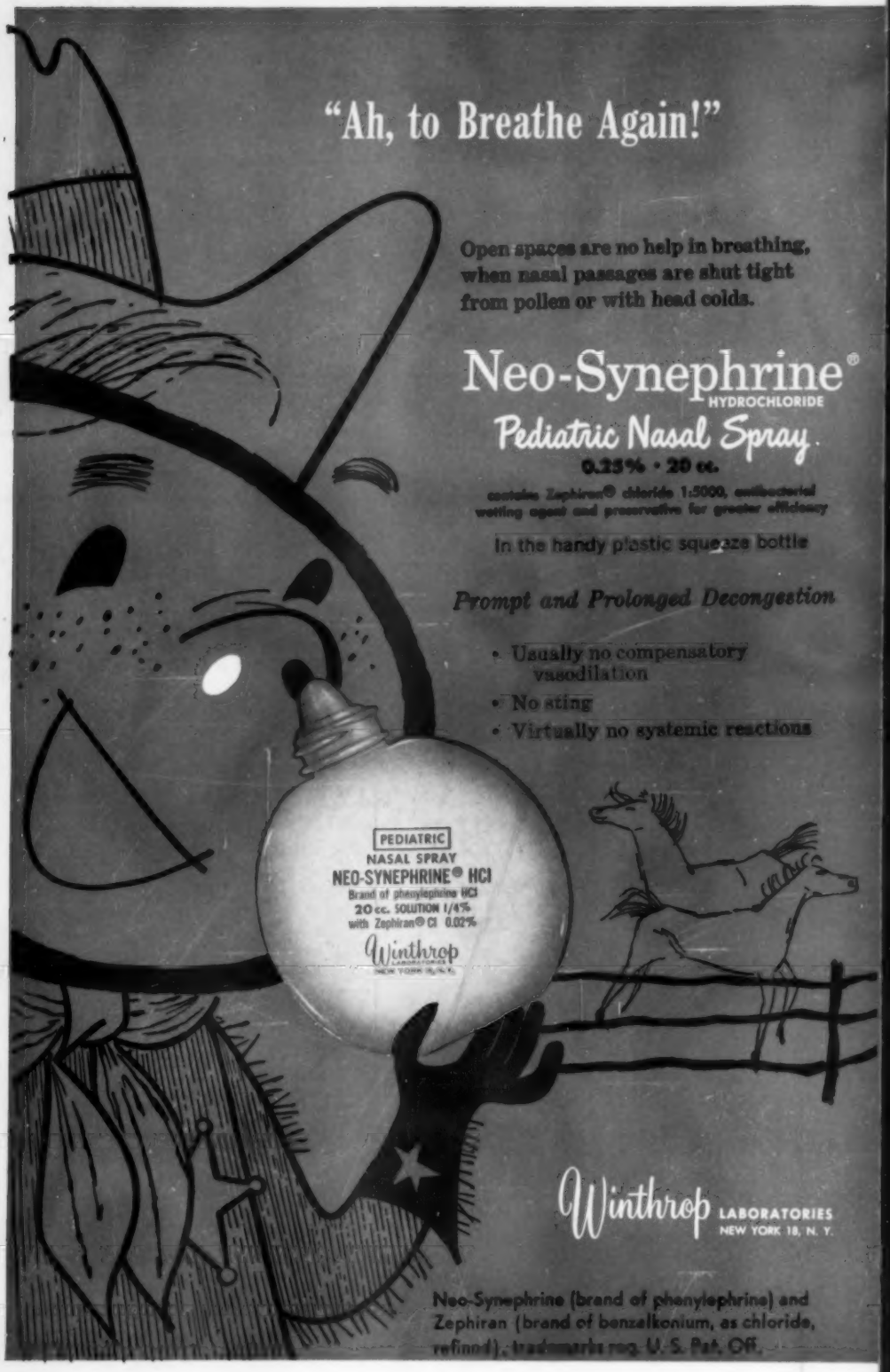
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Neo-Synephrine®
HYDROCHLORIDE
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0.25% · 20 cc.
contains Zephiran® chloride 1:5000, antibacterial wetting agent and preservative for greater efficiency
in the handy plastic squeeze bottle
Prompt and Prolonged Decongestion
• Usually no compensatory vasodilation
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NASAL SPRAY
NEO-SYNEPHRINE® HCl
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